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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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PATIENT ENGAGEMENT ADVISORY COMMITTEE

+ + +

October 12, 2017
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

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DEBORAH CORNWALL, M.B.A.	Committee Member
FREDERICK DOWNS, JR., M.B.A.	Committee Member
BENNET R. DUNLAP, M.S.	Committee Member
AMYE L. LEONG, M.B.A.	Committee Member
SUZANNE SCHRANDT, J.D.	Committee Member
MONICA W. PARKER, M.D.	Committee Member
KATHERINE D. SEELMAN, Ph.D.	Consumer Representative
ROSE BLACKBURNE, M.D., M.B.A.	Industry Representative
LETISE WILLIAMS	Designated Federal Officer

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M E E T I N G

(8:00 a.m.)

MR. CONWAY: Welcome to the second day of the Patient Engagement Advisory Committee of the FDA. This is the second day of our inaugural meeting. And I'd like to go ahead and call this meeting to order. My name is Paul Conway, and I serve as the Chair of the PEAC. I'm also the President of the American Association of Kidney Patients, and I'm a patient of 37 years as a kidney patient, the past 20 years as a kidney transplant patient with an additional 2 years on dialysis.

For the record, I'd like to note that the nonvoting members constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the committee members participating in today's meeting have received training in FDA device law and regulation.

For today's agenda, the Committee will continue its discussion of (1) Patient Involvement in the Design of Clinical Trials; (2) Patient Recruitment, Enrollment, and Retention; and (3) Communication of Study Results to Trial Participants.

Before we begin, I would like to ask our distinguished committee members and fine public servants of the FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And we'll go ahead and start with Dr. Tarver.

DR. TARVER: Dr. Michelle Tarver-Carr, and I am the Acting Assistant Director for Strategic Programs in CDRH.

DR. PARKER: Monica Parker, Director of Minority Engagement, Emory Alzheimer's Disease Research Center, and family physician.

MS. SCHRANDT: Hi, good morning. Suz Schrandt. Professionally, I'm the Director of Patient Engagement for the Arthritis Foundation, and I have a background in health and disability law and policy. And then personally, I have a form of rheumatoid arthritis for

most of my life and so a lot of experience with joint replacements, etc., and more experience to come, I'm sure.

MS. LEONG: Good morning. My name is Amye Leong from Santa Barbara. I am President and CEO of Healthy Motivation, a consultancy in patient advocacy and patient engagement in research. I also serve as Director of Strategic Relations for a United Nations initiative called the Bone and Joint Decade, the Global Alliance for Musculoskeletal Health. I serve as chair of the Arthritis Foundation in California. I am a PCORI, P-C-O-R-I, ambassador. My areas of expertise include translational medicine, motivation, behavioral change, patient advocacy, and outreach to underserved populations.

MS. CHAUHAN: Good morning. Cynthia Chauhan from Wichita, Kansas. I am a survivor of kidney and breast cancer and live with heart failure. I am a patient advocate and representative with particular interest in bringing the patient perspective to the research table and to the professional table.

MR. DOWNS: I'm Fred Downs. I'm the prosthetic consultant for Paralyzed Veterans of America. I was National Director of the Prosthetic and Sensory Aids Service for the VA for 30 years, and I have been in a couple clinical trials and am currently in one right now.

MS. CORNWALL: Didn't get the light, sorry. I'm Deborah Cornwall. I am a breast cancer survivor, 16 years, and I am a long-term volunteer, leadership volunteer, with the American Cancer Society and its Cancer Action Network. Also have written a book based on interviews with over 100 cancer caregivers. And so the perspective that I bring, both from my American Cancer Society activity and from my work as an author, is that of the cancer patient and the cancer caregiver and the family unit, the whole patient.

MR. DUNLAP: Good morning. Bennet Dunlap. I'm a patient advocate for people with diabetes from Bryn Athyn, Pennsylvania.

DR. SEELMAN: Good morning, everybody. My name is Katherine Seelman. I'm

Professor Emerita, University of Pittsburgh School of Health and Rehabilitation Sciences and Associate Dean. I was formerly the Director of the National Institute on Disability and Rehabilitation Research, and one of two Americans who guided the first world report on disability at WHO and the World Bank, and a lifetime user of assistive technology.

DR. BLACKBURNE: Good morning, everyone. Dr. Rose Blackburne. I'm an Executive Medical Director at PPD, Pharmaceutical Product Development, a global CRO, and I'm the Industry Representative. I'm a former practicing obstetrician/gynecologist prior to joining industry about 13 years ago.

MR. CONWAY: I'd like to thank my colleagues for introducing themselves. I think you'll find, as I have over the past several days here and getting to know my fellow committee members, that they draw from many different disciplines and backgrounds, they have a great degree of knowledge and skills, different academia, different -- the medical community, they're from the advocacy community. They have government background, public service background. But I think the common denominator that you will see is that we all have either lived or understand fully the patient experience and everything that goes with that, and we share the same sense of impatience, and I think you'll find that many of our folks here at the table have absolutely no fear in asking the question of "why" about the status quo or viewing things that "if it's to be, it's up to me."

At this point, I'd like to read into the record, again, here on the second day, the actual purpose of the PEAC:

The Committee provides advice to the Commissioner or designee on complex issues relating to medical devices, the regulation of devices, and their use by patients. The Committee may consider topics such as Agency guidance and policies, clinical trial or registry design, patient preference study design, benefit-risk determinations, device labeling, unmet clinical needs, available alternatives, patient-reported outcomes, and

device-related quality of life or health status issues, and other patient-related topics. The Committee will provide relevant skills and perspectives in order to improve communication of benefits, risks, clinical outcomes, and increase integration of patient perspectives into the regulatory process for medical devices. It will perform its duties by discussing and providing advice and recommendation in ways such as identifying new approaches, promoting innovation, recognizing unforeseen risks or barriers, and identifying unintended consequences that could result from FDA policy.

At this point, I'd like to ask the members of the audience, if you've not already done so, to please go ahead and sign the attendance sheets that are located on the registration table directly outside the meeting room.

At this point, I'd like to introduce Ms. Letise Williams, the Designated Federal Officer for the Patient Engagement Advisory Committee. She will make some introductory remarks.

Letise.

MS. WILLIAMS: Good morning. Thank you, Mr. Conway.

I will now read the FDA Conflict of Interest Disclosure Statement: The Food and Drug Administration is convening today's meeting of the Patient Engagement Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members of this Committee serve as special Government employees. Members and the Chair of this Committee were selected by the Commissioner of the Food and Drug Administration or their designee. They are knowledgeable in areas of clinical research, primary care patient experience, and healthcare needs of patient groups in the United States, or are experienced in the work of patient and health professional organizations. They have methodology for eliciting patient practices and strategies for communicating benefits, risks, and clinical outcomes to patient and

research subjects.

The purpose of today's meeting is to discuss and make recommendations on the topic of patient input into medical device clinical trials. This meeting provides the opportunity to bring patients, patient organizations, FDA, industry, and other medical and scientific experts together for a broader discussion on this important patient-related issue. The discussions are exclusive of any particular product or a class of products, and we'll not seek advice on a regulatory decision or action. Therefore, this meeting does not involve deliberation, decision, or action that is focused upon the interest of specific parties or discrete and identifiable class of products, and accordingly, it has been categorized as a meeting involving a non-particular matter.

Again, I'd like to mention that Dr. Rose Blackburne is serving as the Industry Representative for clinical trial design, conduct, and analysis, and is acting on behalf of all related industry. She is employed by Pharmaceutical Product Development, LLC.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript. Thank you.

But before I turn this meeting back over to Mr. Conway, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting and handouts for today's presentations are available at the registration table outside the meeting room.

The press contact for today's meeting is Stephanie Caccomo.

I would like to remind everyone that members of the public and the press are not permitted in the Committee area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the committee meeting has

concluded.

If you are presenting in the Open Public Hearing session and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with AnnMarie Williams at the registration table.

In order to help the transcriptionist identify who is speaking, please be sure to identify yourself each and every time that you speak.

For the record, FDA has received two written comments which are provided to the panelists, and a copy is also available at the registration table.

If anyone in the audience has questions or needs assistance, please see an FDA staff member. FDA staff members are wearing FDA name tags.

Finally, I'd like to ask that everyone please silence your cell phones and other electronic devices at this time.

Thank you.

Mr. Conway.

MR. CONWAY: Thanks, Letise.

We'll now hear a brief update on CDRH and Patient Engagement Efforts from Ms. Katie O'Callaghan of the FDA. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Committee Chair.

Ms. O'Callaghan, you may now begin your remarks.

MS. O'CALLAGHAN: Good morning, and thank you. Thank you to all of the members of the Committee and Mr. Conway for all of the work that you do on behalf of patients every day, but also for agreeing to serve in this capacity. I'd also like to take one moment to acknowledge the hard work and dedication of all the FDA staff who have been a part of making this possible. In particular, Ms. Letise Williams, Susan Chittooran, and Annie Saha,

Ken Skodacek, Lisa Miller, and the leadership of Dr. Michelle Tarver for pulling this all together. They truly embody our "Patients First" motto at FDA, and thank you for that.

As has been discussed by the previous FDA speakers, patients really are at the heart of all that we do, but this is true not just for the FDA employees here, that's certainly true for industry, for healthcare professionals, for all those working in patient organizations and others, so it's a common purpose in many ways. And the CDRH vision has been put up on the screen before you, as well, and the point I'd like to emphasize here is that perhaps it seems obvious that patients should be front and center in all the work that we do, but I'd like to take one moment to provide some historical context about what's a little bit different in the medical device world that gives some explanation to this.

So many of the early medical technology innovations that were true breakthroughs and have had dramatic impacts on health were life saving, and they were typically tools that were in the hands of clinicians, oftentimes surgeons. And so the questions about what a patient's preference might be and what outcomes in terms of quality of life and so on were important were less in focus at that time, given the state of health and medicine and technology. When we fast-forward to today, we realize that some of the challenges that we face in the healthcare ecosystem are a result, in part, of our successes. We have had dramatic reductions in death rate from a lot of conditions that are due in part to the successful advances in medicine and health technologies. But what this means is that we have more and more Americans living rather than dying from diseases, many are living with chronic conditions, by some counts over 100 million Americans living with chronic conditions.

And so patients today have a different role in healthcare and in managing their own health. We have more patients involved in shared decision making with healthcare professionals and their care team and in disease management long term. We increasingly

see patients using devices themselves, oftentimes at home. And patients, of course, communicate and connect to share information and gather their learned wisdom across a group of patients, other real-world patients, who are like them and living with their conditions and challenges. And so with this perspective in mind, we feel that this is not just a nice to-do. In today's reality, safe and effective medical device use increasingly depends on effective patient engagement.

CDRH as well as other centers across the FDA and other organizations across the healthcare ecosystem have been working to give patients a greater voice in the work that we do and the impacts of that work on the American public. This all leads to increasing scientific understanding in what works best for diagnosis, treatment, and management of disease, how people regain health, and also, as Dr. Owen Faris mentioned in his remarks yesterday, helps FDA to better convey information in a useful format to make patients and clinicians -- to help patients and clinicians make more informed and personalized choices.

Dr. Shuren gave an overview yesterday of some of our accomplishments and the work that's ongoing at CDRH as part of our strategic priorities. I'll expand on this in the next few slides.

As we were taking stock of our accomplishments and the challenges before us of where we've come from and where we needed to go as an organization, there is broad recognition amongst the leadership team and throughout the organization that it was time to go beyond all of the great work that our staff do every day on behalf of patients and find ways to work more with them as partners to protect the safety of patients and to promote beneficial innovation. And this is reflected in the commitment, one of our three priorities to partner with patients.

And we had a two-prong strategy for achieving this. The first is to promote a culture of meaningful engagement by facilitating CDRH interaction with patients, so focusing on

patient engagement, and the second is to increase the use and transparency of patient input as evidenced in our decision making, recognizing that if we didn't move beyond the patient engagement to actually move tangible information into our decision making, we would not have completed the job.

So our focus, first, on the patient engagement goal: A lot of the culture change in patient engagement was to begin with interaction, recognizing that while many of us are patients, a patient with diabetes like Owen Faris may not have the depth of appreciation of experience in a patient with heart failure. And so by facilitating interactions with all of our staff to have an opportunity to hear from patients living with the conditions that would be affected by the technologies we're evaluating, we can provide important context within which our FDA staff, then, evaluate the benefits and risks of different technologies. So far we are doing very well in that department. We have -- 85% of all of our employees at CDRH have had an interaction since we began this effort with patients.

But moving from those interactions into a meaningful engagement was part of the natural maturation process of moving towards a culture of patient engagement. Some of the work that we have ongoing is putting processes in place to make it easier for staff to do this as a routine part of their work, and particularly focusing on ways in which patient input can be sought out that is particularly relevant to the job at hand.

And then moving on from meaningful engagement into true partnership and, of course, this meeting is a prime example of that, where the various organizations and key leaders in their field come together and agree to work on some of the systemic obstacles to better health and wellbeing of patients.

This is a bit of a commercial: One of our upcoming organizational events that is part of our culture change effort is the CDRH Patient Organization Awareness Day, and the reason we thought that this was an important thing to do is that while there's a lot of

recognition throughout the organization about the important work of healthcare professional and scientific professional organizations, there was generally less awareness about the work that patient organizations do, and we thought what better way to raise that awareness than to bring the patient organizations in-house to speak with and meet our employees. So as I said, this is a commercial, so this is primarily a request for patient organizations who would be interested in participating in this to contact Lisa Miller and Noel at the address noted there.

I mentioned our second goal was to increase the use and transparency of patient input as evidence in our decision making. I'm going to take one moment before diving into that to just put a little bit of definition around some of these terms that we're discussing here today.

Patient input: So as we began our work and talked to different stakeholders and decision makers throughout the ecosystem, we realized there was somewhat of a tendency in some to discount patient input as anecdotal and subjective and to instead rely on a desire to rely on hard, clinical, objective evidence, when in reality we recognize that "let's take clinical evidence first," we have a range of types of clinical evidence. You might have anecdotal clinician experience, you might have the perspectives of key opinion leaders in the clinical field who have amassed a depth and breadth of understanding in a particular area, you may have observational studies, and you may have the gold standard, randomized clinical trial with masking or blinding.

So there's really a range of types and qualities of clinical evidence, all of which are important, and what's critical to FDA's decision making is to use the right information for the right purpose; fit-for-purpose is a term we use for this. But the same is true for patient input. You can have patient input that ranges that gamut. And so I'll focus for a moment on two particular types of patient input that are at the more rigorous study, prospective study

end of the spectrum: patient-reported outcomes and patient preference information.

Patient-reported outcomes many are familiar with, or PROs. These are things that are oftentimes collected in clinical study protocols alongside other types of evidence and are reported directly from patients typically reflecting things like symptoms, function, psychological well-being, or quality of life.

Patient preference information is a relatively newer term in this arena, although the science has been around for quite some time, and this has been recently more -- more recently adapted to the healthcare setting. This has to do with how a person, particularly a patient with a condition, thinks about the tradeoffs between benefits and risks when making decisions.

So what are we dealing with? We have seen a significant increase in the patient perspective studies submitted to FDA. So our team took a look at the historical amount of patient-reported outcomes that the Center has seen, and from the time that the Agency released a guidance on patient-reported outcomes in 2009, we've seen a 500 -- over 500% increase in the number of submissions with that information. More recently, in the last two fiscal years, that number has continued to increase. We've seen an 80% increase, and this is in patient perspective studies overall, so it includes patient preference information as well.

Many previous speakers have shown this figure, which we use to depict the total product life cycle. I will focus in on the portion of that with which -- that is more strictly within FDA's purview for decision making that you see here, and what have we done to increase the use of patient input as evidence? We have issued numerous final guidance, which I will briefly touch on, and implemented that. We are hiring and training staff in these areas of patient input as evidence. We're broadening our access to subject matter experts in these fields and expanding our collaborative networks to enable us to do

research and further the science.

So the clinical decision point, particularly relevant for today's discussion, we have implemented final guidance around use of patient preference information in the IDEs, which is the clinical trial application that we look at, and there's the guidance I mentioned which describes PROs and other outcomes that matter most to patients.

At the regulatory decision point, we have patient preferences and PROs that can be used in marketing applications that FDA looks at when weighting the benefits and risks. And we also have, in the postmarket arena, patient preference that can be considered in compliance benefit-risk, as well as patient preference information in PROs for new or expanded uses of technologies, also referred to as label expansions.

Jeff touched on how patient preferences contribute to regulatory decisions for medical devices. I won't reiterate all of that here, but it's here for reference and for those of you in the audience. And we also have numerous ongoing studies, and I'll point out that at the bottom section of the slide there in a variety of different clinical and technological areas.

From here, we're building on progress together in MDUFA IV, the user fee agreements that were reached between FDA and industry. There was a joint agreement to invest in the progress we have made in these three areas, patient input in clinical trials, of course, being one.

And so here is simply a schematic of the phases of the clinical trial process that we are discussing today, and one thing that we have -- we've gone through the cultural change efforts within the organization is that describing this not as an additional thing to add into the process but as part of a solution to the challenges we are already trying to overcome has been particularly helpful.

So thank you for your attention, and I'll turn it back over to you, Mr. Conway.

MR. CONWAY: Great. Thank you very much, Ms. O'Callaghan.

At this point, we'll hear a recap of Day 1 from Dr. Tarver.

DR. TARVER: Good morning. So I've been charged with giving a recap of Day Number 1, and I want to begin first by reiterating some of the points that were raised by the speakers.

On Day 1 we heard from Dr. Faris, who told you that he understands what it's like to be a patient as well, and how his experience has been with medical devices. And I think that's an important point that was emphasized, that we are, at CDRH -- our staff, our reviewers -- are patients, are care partners, and are reviewers, and so we have a dedication to ensuring that the devices that hit the market are safe and effective because it affects ourselves and our loved ones.

The other point that I think was highlighted, that we have a commitment to engage in patients. Dr. Shuren told you about all the initiatives, and Ms. O'Callaghan also alluded to all the initiatives that we have undertaken at our Center to involve the patient's voice in our regulatory decision making. And this inaugural meeting is one reflection of that commitment to engagement.

Another commitment to engagement is the format that we used on the first day. It's a format that has not been previously used in Advisory Committee meetings, and it was a format that allowed for engagement. The audience sat at tables and were able to engage around a hypothetical scenario. FDA staff were moderators and note-takers. By their very roles, they were in listening mode. We wanted to hear what patients had to say, what care partners had to say, and what industry's experience has been with the engagement efforts. As they reported out to the Committee, they reflected the conversations that were held at the table so that you could hear what we, as FDA, heard.

And so today I'm going to recap some of the round table discussions that you all did

not have the privilege of hearing. I collected all the notes from the 10 or more tables that were assembled here in the room, and I looked for overarching themes that I will cover today.

For those of you who were not with us yesterday, the round table discussion was based on a hypothetical scenario that looked at ways that we could engage patients from the design phase, through the conduct of the trial, and then how can we communicate results when the trial doesn't turn out as we may like. The tables, as I said before, were comprised of patients, patient advocacy group representatives, industry members, and listening FDA staff.

So I wanted to cover the first theme that emerged that transcended all the different scenarios that the patients and the audience members were discussing yesterday. The first one was perceived barriers to engagement. A number of the tables mentioned concerns about the legal ramifications of engagement. They also echoed concerns that regulatory barriers maybe exist in the engagement process. And one of the points one of the tables mentioned is that perhaps by engaging patients, it may change the quality of the data. And so these are perceptions that we need to revisit and discuss today and perhaps change.

There was also a concern about privacy and how to protect patients' privacy, as well as the proprietary information of the industry members. And that is another discussion that we hopefully will touch on later today.

And the last point that came up was the return on investment. The return on investment was not limited to the industry members but also to the patients that are participating. There is a time and a cost for all parties involved in the development and conduct of trials and that came up in our discussions.

So I'm going to start with the first scenario that the audience members tackled, and that is how to involve patients in the design of clinical trials. The first point that emerged

out of that discussion, that is, it's important to understand the patient perspective and the patient population in order to humanize a clinical trial, to understand what challenges patients may face, and conduct of the trial requires a conversation with them prior to the design.

So the two questions, sub-questions, that the audience members discussed further is, one, where do you find those patients, and secondly, once you find them, how do you engage them in the design of the trial? A number of tables mentioned that providers, particularly general practitioners, were instrumental in identifying patients and pointing them towards trials and creating networks between surgeons who are often implanting the devices but have very short-term care trajectories with patients and integrating that conversation with general practitioners that take care of patients over their life.

Another point that was raised is the importance of incorporating patient advocacy groups in the conversation. They have access to rich patient networks that could be very useful in designing trials, although some of the tables did raise some concerns. Some of the industry members thought there could be biases by certain advocacy groups that may impact the trial design components. There's also a concern that some patients who participate in patient advocacy efforts are skewed towards a particular demographic and may not represent all patients with that condition. There was a statement that one table mentioned, which is that it's important for the sponsors to initiate the contact, to reach out to patients and find mechanisms in which to do that.

So once you've identified the patient, how do you engage them in the conversation? Some of the tables mentioned that, first and foremost, it's important to set expectations and to clarify motivations. Everyone at the table should know what's expected of them and why they're there.

The other important point that was raised is the importance of education bilaterally.

There needs to be fluency in language between the patients, the providers, the industry members, and the protocol designers because we all speak different languages and all of our voices are important.

The last point that was mentioned during that discussion was the issue of trust, and this issue of trust actually transcends many stages of the trial design. In the design phase, it was mentioned in terms of the patients are sharing very personal information and how is their privacy going to be protected. And then for the industry members, there was concern over the proprietary information that they're sharing and how is that going to be protected. So trying to transform mistrust to trust is an important element in this conversation that happened yesterday.

This spills over to the next phase that they were asked to talk about, which is recruitment, enrollment, and retention. One very important point that one table raised is that when we recruit, enroll, and retain patients, we are not recruiting and enrolling and retaining one person, but a family unit, their care partner, and every other support network that they have around them. And having that awareness, we are informed how to best design our trials as well as how to encourage enrollment and retention within that trial.

So one of the other points that came up as we talked about trust is developing communities of trust and leveraging those communities of trust. Many tables mentioned finding patients of diverse backgrounds at churches and social groups and reconnecting again, as we mentioned before, with the general practitioner. This will help create diversity within our trials and ensure that we have study populations that are representative of the patient population.

The other message that came out of the discussions was awareness of clinical trials as a care option. A lot of tables mentioned that patients did not know that a trial was available to them, first, and secondly, that that could be a care option for them. And

involving them in the conversation may help increase participation in trials.

The other point that was raised is the importance of focusing on the patients and not just on trial goals. And that was mentioned at a number of tables, that the messaging is important to make patients feel valued in trials and that they are contributing to the science and the heath of the U.S. public.

The last point that was touched on in terms of this topic was minimizing the burdens and augmenting the comforts. There were a number of burdens that were identified at the tables; those included travel, the timing of the visits, what time of day they are and whether patients had to work and what the burden of missing work would be on them. The cost of getting to the trial, parking, food while they're spending the entire day there, how long the trial duration lasts, and the timing of incentives. Are they getting an incentive at the very end of their trial commitment or along the way? They mentioned a lot of patients have altruistic motivations, and to encourage that and communicate frankly with them will help make them feel like they are living up to the principle that motivated them to participate in the first place.

And then also being very sensitive to family obligations: That was mentioned at a number of tables and was mentioned as one of the barriers as to why younger patients, patients from low socioeconomic status, and women may be less represented in some trials.

The other, in terms of augmenting the comfort, so I talked about the burdens. Augmenting the comforts, which stretches to finding other ways to collect data, such as wearables, electronic data capture, electronic patient-reported outcome measures, and other ways to minimize the amount of time they're spending in the clinic and decreasing the frequency of clinic visits.

A number of tables mentioned the importance of small courtesies: thank-yous,

considerate staff, and having a conversation with patients so they feel that they know what's happening and it's not just being done to them.

The last part of this slide focuses on the preparation and anticipation to lead to increased success. A number of tables mentioned the challenges of not considering the developmental paradigm when you're dealing with a pediatric trial, that if it's a 2-year study, children change quite a bit in 2 years, and what's important and what should be measured may vary over that period of time, so it's important to anticipate these things and plan for them so that you can incentivize differently to retain them within the trial.

The last topic that the tables discussed was the dissemination of the trial data and results. Every single table mentioned the importance of closure for patients. The patients have given a significant amount of time to the participation in the trial, they've given a lot of resources, and they want to see that it was beneficial, that it added to our scientific knowledge. And so communication of the results was agreed to by all, but the question that was raised was how do we do that? Some tables mentioned creating benchmarks where patients could match themselves to other patients to see how they did in the trial, but the question that came from that is, well, when do you do that? A lot of tables mentioned the importance of considering communication in the protocol design phase, as well as in the informed consent documents as to how are you going to communicate the trial results and whether you're going to share those results and the data of that individual patient back to the patient.

And then lastly, the theme that emerged at every table was literacy and health literacy, which are not synonymous, as well as numeracy and how to present data in a way that is understandable to patients and allow them to feel empowered with that information.

Privacy concerns also came up in terms of how we share information, and many

vehicles of sharing were mentioned at the tables, including social media, websites, patient advisory boards, and using those healthcare providers again to help send the message around.

So I want to thank you for your attention, and I look forward to today's discussion to help embellish on some of these themes that emerged from our round table discussions.

Thank you, Mr. Conway.

MR. CONWAY: Thanks, Dr. Tarver. And I'd like to just take a minute and say that the Committee really appreciates the efforts of CDRH, the presentation yesterday from Dr. Shuren, from Dr. Faris, Ms. O'Callaghan's presentation this morning, because I think what you've been able to do is, in front of the Committee and in front of the public, outline what the strategic vision is, the tactics that you're using to engage patients, the metrics that you have, and also our role in that process, and I can assure you that the Committee is very enthusiastic to help you meet those goals.

Next, we'll hear a presentation pertaining to Topic Number 1, Patient Involvement in the Design of Clinical Trials, beginning with a presentation by AstraZeneca.

MS. O'BRIEN: Good morning, my name is Faye O'Brien, and I am a program director at AstraZeneca's Global Medicines Development Group. I want to thank the FDA organizers for the invitation to be here today and to present the Committee with an overview of how we involve patients in our design of clinical programs.

So we all know that patients are becoming more and more educated about their disease, and they're involved in their treatment choices. We also know that similarly, the role of patients in the conduct of clinical trials is evolving. We no longer can think of patients simply as a clinical trial resource. When they're engaged, they can be partners, advocates, contributors, and winners in the process.

Now, this is not just good for the patients but also for the sponsors as it will lead to

improved clinical design, improved recruitment, retention, and compliance. At AstraZeneca, putting the patients first is one of our five core values.

Our patient-centered research framework at AstraZeneca starts with the study planning and then carries through the duration of the study and study conduct, and it continues post-study. Today I will focus on the study planning phase and provide you with an overview of two techniques, new techniques, that we have implemented at AstraZeneca to obtain patient input during the planning phase. They include online patient community research and study visit simulation.

So let's start with obtaining feedback through social media. PatientsLikeMe is an online community where patients can share their medical data, track their progress, and also interact with other patients. Through AstraZeneca's partnership with PatientsLikeMe, our study teams are able to see patient-generated health data and focus on impact on symptoms, outcomes that matter to patients, and how patients describe disease experiences.

In addition, we are able to field surveys via this patient community where we can test our protocol concepts before they're finalized. So we're specifically interested in terms of anticipated patient sentiment around participation. To date, we have utilized this format for over 12 of our programs with input from over 2,000 patients, resulting in improved study design, more clear study material, and improved study experience for our patients.

In May 2014, we were working on a final protocol of a global Phase III lupus program. Lupus studies are quite complex, and at the time, two very large Phase III global programs by other sponsors had failed, so it was a crushing disappointment to the lupus community and with a concern about starting our Phase III program.

So we generated this hypothesis that when engaging patients, we could better navigate the challenging lupus trial environment at the time and transform the patient

experience from simply being subjects to contributors and advocates. So we decided to test a draft protocol with actual patients in an actual clinical setting before the protocol was finalized. To our knowledge, this is the first time that this has ever been done in the industry.

So initially, we selected a site in Altoona, Pennsylvania, but soon we quickly decided to add a second site, realizing that we didn't have adequate representation of African-American patients in our study. A total of 18 patients participated in our mock trial. The manuscript associated with this pilot was published this summer in the *Patient Preference and Adherence* journal.

The participating sites tried to match the inclusion/exclusion criteria listed in the draft protocol. The patients signed participation agreements and consented to be interviewed at the end of each mock visit. Please note that this was not the actual clinical trial. We were just testing the protocol in a simulated, on-site, in-clinical setting format. We provided the sites with simulation playbooks so they know what to do during those visits.

The patients underwent two key mock study visits, this was an infusion study, 4- to 6-hour visits, really complicated protocol. So the patients went through this mock visit, and at the end of each visit, we administered a structured administrative survey and a structured interview, and then we captured those learnings.

To facilitate the patient interviews and subsequent analysis, we developed an analytical approach based on the framework developed by the Picker Institute and the Institute of Medicine. The Institute of Medicine maps eight dimensions of patient-centricity. We distilled those dimensions into four domains so we can capture the impact of our patient-centricity approach in our clinical trial. They're listed here: information, communication, and education; responsiveness to needs; access to and coordination of

care; and continuity and transition.

We learned a lot from this exercise. Lots of recommendations, lots of changes to the protocol. We changed our procedures, which reduced the frequency of procedures. We reduced the duration of a procedure. We confirmed the patient-reported outcomes that were going to be used in this study. We also learned a lot about what the sites can do better to provide comfort to the patients. So we implemented a large number of those recommendations, and we continue to implement those recommendations in other trials, not just lupus, but other diseases and therapeutic areas. Today, I'm just going to walk you through a few of those learnings.

So under information, communication, and education front, it doesn't surprise any of us that patients could be overwhelmed with the amount and complexity of information that they receive at each visit. In particular, the consent form can be overwhelming. All the patients express comfort with their level of understanding; it really varies in content and depth. If the patients do not consider how study participation affects their lives, the reality of participation can be dissatisfying to them, influencing how to complete the patient-reported outcomes or even they might drop out. So we recommended 33 recommendations to the team on this one domain. The most important one is to provide more time between providing the patients with consent information and actually obtaining consent. Let's make sure that there is enough time to mull this over, understand what it takes to be a part of the study. Let's make sure the consent forms are simple and easy to understand. Let's provide them with study information and consent forms that are electronic, that definitions are embedded in the consent form, that it actually has an audio component so they can hear what they're consenting to. Let's make sure that we are reaffirming their consent throughout the study, make sure that they're comfortable and they understand what's next for them in the following visits. And also, let's make sure to

encourage involvement from family and friends where it's possible to allow them to better understand what has been consented to.

Next, I'm going to take you to "Responsive to Needs." Now, the degree of disruption to patients' lives due to study participation is important to patients' propensity to enroll and continue in the study. A visit lasting more than half a day may require vacation time by patients, while for others it really results in loss of income, so effectively excluding patients who work or patients from the lower socioeconomic groups.

So some of the recommendations that we provided to the teams include for -- really, for sponsors to formalize a process for scrutinizing the schedule of events. Let's make sure that this is a step on the checklist. As the sponsors are finalizing their protocol, did we pressure test the schedule of events? Did we need all of these procedures? Did we need them in the frequency stated? And let's remove procedures that are not needed for the label. These are just, you know, they're nice to have procedures; let's make sure that they're removed from the protocol. Let's make sure that the sites establish a total visit duration and they make that commitment to the patient. So you come for this visit, it's going to take you 3 hours, and let's make sure they're out after 3 hours. And also, let's consider if and how visits could be split, let's say into two visits, without causing disruption to the data and the study coordinator's planning, and let's provide the sites with guidance on how to split a visit without triggering monitoring or queries. So that flexibility, in terms of a patient that needs to, let's say, have a visit split into 2 days in order for them to come to the visit.

Continuity and transition: We heard this over and over again; patients want feedback real time on the assessments that they've undergone through the course of their clinical visits, and they want to know how those assessments are impacting their everyday illness. So satisfying this informational need of patients will increase engagement, and the

possibility of greater insights into one's health and condition could be a deciding factor in participation and retention.

Our recommendations were that the investigators should provide a verbal or printed summary of lab results and implications under patients' illness on an ongoing basis at every visit. We also recommended the teams to provide regular, let's say quarterly, readout on study progress designed for the participating patients. We all are familiar with site newsletters. Let's go ahead and put together patient newsletters.

I would like to just highlight an internally developed tool at AstraZeneca where we piloted this tool at the lupus simulation, and since then, we have incorporated it in dozens of studies. So TRACE is an online system that transforms the study material into patient-friendly content. It basically takes the informed consent forms, study protocol, other supporting documents, takes it from the scientific speak to the everyday language, and this is actually done via just a simple click, and creates patient websites, patient booklets, and patient apps. And this tool can be used for any trial, and it can be used in any language.

In summary, putting patients first means delivering for patients with patients. It starts with collecting insights. Now, there are many ways of collecting this insight; let's not do it in silos. We can use the patient advisory boards, observation visits, patient community forums, patient interviews, and simulations, as I described. And then let's take these learnings into co-creation of the protocol and consent from the patients. And as hard as it might be, let's figure out a way to measure the effectiveness, and yes, ROI is important; so is measuring the patient's experience. And maybe that is not really transferable into an ROI. So that's an evolving field in terms of measurements, and it's an area of focus for AstraZeneca.

And with that, I want to thank you for your attention.

MR. CONWAY: Thank you very much, Ms. O'Brien.

(Applause.)

MR. CONWAY: We'll now hear a presentation from the National Cancer Institute.

MR. FREIMUTH: Good morning, everyone. Thank you so much for having me. This is very exciting for our office, and we're thrilled to be a part of it. So a special thanks to Lisa Miller and Susan Chittooran for kind of helping us -- informed us about the Committee as we craft our presentation today.

My name is John. I work for the National Cancer Institute's Office of Advocacy Relations, and I'll be talking today a little bit about what our office does and how NCI engages advocates throughout the -- kind of throughout clinical trials within NCI.

So our office was founded in the late '90s in response to the advocacy community wanting -- understandably wanting a seat at the table to have input in clinical trials. As you can imagine, over the past 20 years, the advocacy community has evolved and grown, which is great, and so has our office evolved a little bit in response to the advocacy community, as well as in an effort to make sure we're serving the needs of the institute.

We work with individual research advocates who are people who typically have a personal connection to cancer either as a patient or a caregiver; in some instances extensive professional experience also. They typically have some basic understanding of clinical trials and the science, and the advocates that we are fortunate enough to work with, typically they have what we call the collective patient perspective, so they represent large constituencies, and they're able to not only share their personal experience but also serve as the voice for, kind of, their entire community. Some represent a specific cancer type or organ, say, for instance, pancreatic cancer or bladder cancer, whereas others specialize in a certain topic, for instance, financial, toxicity, health disparities, or clinical trial design.

In addition to working with individual research advocates, our office also works with national and local advocacy organizations to help identify our areas for collaboration and

for partnership both with the NCI as well as with each other, in terms of the advocacy organizations. So we're always happy to kind of help connect the dots or play matchmaker, so to speak, for collaborations.

Most importantly, the goal of our office is to ensure the collective patient perspective is embedded in our -- really, throughout the whole NCI to advance cancer research and improve patient outcomes. We're fortunate enough to sit within the Office of the Director, which is currently acting director Dr. Douglas Lowy. And so we are very fortunate that we have that gateway to NCI leadership, so we can listen to -- you know -- is top in mind of advocates and communicate that to leadership, and that's really how we always want to think of our office, as a relationship-based office, one where advocates feel comfortable coming to us expressing what their concerns are, and then we can very quickly, you know, elevate that to leadership.

So our office works to involve patients in a variety of ways across the institute, as I mentioned. However, for the purposes of this presentation, I'll really try to focus just on how we engage advocates in clinical trials, obviously, since that's the focus here. So I'm going to touch on the top three -- these are just a few of the ways in which we do involve advocates in clinical trials. I'm going to kind of quickly touch on the top three since I'll be going into a little bit more depth later on, on those.

But just very quickly, our National Council of Research Advocates, this is our federal advisory committee that's comprised solely of cancer research advocates. Currently, there are 13 members. We meet typically three times a year, and we discuss topics that are top of mind for NCI leadership that they're really looking for input on from the advocacy community kind of at the beginning of the initiatives.

Our National Clinical Trials Network is our externally funded network responsible for clinical trials. They do a lot of our precision medicine portfolio.

The scientific steering committees and task forces sit within NCI, and they kind of guide with the National Clinical Trials Network Phase II and Phase III concepts.

I want to definitely mention the Division of Extramural Activities. What they do is, you know, every application that comes in through DEA actually does get reviewed by a patient advocate. So they really have -- and they do a peer review. So they really have a hand in even what gets funded externally and what doesn't, which is certainly great.

And then also our Clinical Trials and Translational Research Advisory Committee, this is our external oversight committee that really advises NCI in its clinical and translational portfolios, very much kind of on that 50,000-foot level.

So as I mentioned, I'm going to go a little bit in depth on the National Clinical Trials Network and how that engages advocates. I put up this slide just to kind of give you an idea of what the structure of NCTN looks like. As you can see, these are the different groups, that they're acronym-heavy groups, but the groups that develop typically Phase II and Phase III clinical trials. Each NCTN group has their own patient advocacy committee, so advocates are really involved throughout the entire process.

So this is a summarized list of some of the areas -- I apologize. This is some of the lists -- these are lists of just a summary of some of the areas in which advocates do, you know, provide input on throughout the clinical trials process. They really look at the broad scope of what research is being done in that area of the committee that they sit on. They look at, you know, what's being done and what's not being done, what research do these advocates want to see being done and where are those gaps.

They certainly look over the informed consent, which I know is something that we discussed here and has been a part of the presentations. You know, is the informed consent readable? Is it appropriate language for patients? Is it, you know, overly scientific? One thing we've been hearing a lot about is, you know, patients will all ask, you know, does

the informed consent clearly outline the financial burdens? You know, what is going to be covered by the trial? What do patients need to go back and talk to their insurers about?

Eligibility criteria is a major one that's been receiving a lot more attention recently, issues of exclusivity. Are the criteria too restrictive? You know, they look at generalizability. One example is cardiovascular, people with cardiovascular issues, typically it's been an exclusion criteria for some oncology drugs, and it's a matter of really looking at it. You know, is that appropriate? What is there for patients who have cardiovascular issues, once a drug is approved, if they, you know, need oncology drugs?

You know, making sure also that no criteria exists that would unintentionally or disproportionately screen out minority or other underrepresented populations is something that advocates typically really closely look at.

In terms of the study design, advocates typically ask a lot about the study schedule, are all the procedures necessary? Can any of the visits be dropped to make it more logistically easy or less invasive for patients, while still collecting the appropriate data?

Advocates also look at equipoise. Are there differences among the arms of the trial compared with each other and the standard of care? Are they really truly different? If one specific -- you know, if one specific treatment throughout the trial emerges as overwhelmingly more effective, you know, are patients going to be allowed to cross over? And if so, you know, when is that decision going to be made? How far along, you know, how much preliminary data is needed?

They also look very much at patient-facing materials, you know, whether it's recruitment materials, press releases, informational videos. Things that really reach the patient really should be reviewed by the patient.

Accrual plans: Obviously, you know, promotion, which organizations to reach out to, how to ensure underrepresented populations are included in the study and are recruited to

the study.

Outcome data: I think that it's kind of been a common theme throughout the last day or so is that, you know, patients look at, you know, are these outcomes really outcomes patients want? Are they really outcomes that will help patients?

And advocates also sit on data safety monitoring boards and are involved in dissemination to their constituencies, advocacy groups that they may represent.

And, you know, this is something that we -- these are areas that are really -- advocates are involved in pretty much across the board. There are some, you know -- there are some points where this is kind of our gold standard of what we want. I think that it is, for the most part, happening, but it's something that we are always looking for opportunities in these areas for advocate input on.

So once a concept comes from the National Clinical Trial group, network group, and then comes to NCI, it goes to our scientific steering committees which are composed of leading cancer experts and advocates from outside the institute, as well as senior investigators within NCI who meet regularly to evaluate the clinical trial concepts and set disease-specific strategic priorities and they really -- you know, much of it is that portfolio analysis, what's being done and what's coming out of the other NCTN groups. It's designed to create community involvement in the clinical trial design, really evaluate and provide input into the design and implementation, and I think it's definitely worth mentioning that patient advocates are voting members, so they do have a say in, kind of, what goes through.

In addition, all the advocates who sit on scientific steering committees sit on an additional committee called the Patient Advocate Steering Committee, and that's a committee designed solely, as you can imagine, for patient advocates, and it's where they discuss issues that come up in the scientific steering committee meetings. They also discuss other things that are kind of top of mind for advocates, major issues coming out. And they

also have educational presentations. You know, we hear sometimes, the advocates will say it's intimidating sitting in a scientific steering committee or a task force, that it's overwhelming to listen to, you know, so many scientists talk. And, you know, so we -- you know, some of the educational components through that, they do presentations on things like virus statistics and that sort of thing to help just kind of make advocates feel a little bit more comfortable.

And I think that that's something that our office really strives to do each and every day, is to make sure that any advocate who is involved in NCI initiatives, that they feel that they can come to us, express any concerns, say, hey, I'd like some more orientation or some more support in this area, and we can provide that orientation or sometimes that can be just connecting them with a more seasoned advocate who's maybe been at this 15, 20 years who can kind of help guide them through the process in some sort of a mentoring capacity.

So, in addition, I also want to mention we -- our office does do post-activity evaluations with both program staff and advocates. And, you know, we have gotten a great -- some great data out of the evaluations with advocates about what's working, what we can improve upon, you know, both with our office and program staff. We want to make sure that each engagement with NCI is a positive one and that we can kind of build on that to continue to involve advocates and make sure that they feel welcome to the table. And also, that their input is obviously valued, certainly.

And I've heard this -- this is, as I mentioned, our National Council of Research Advocates. They focus on matters that facilitate research and often identify and respond to the challenges facing the institute at the request of NCI leadership. NCRA really advises the director on the breadth of all of NCI's work, but sometimes they do focus on clinical trials. For instance, our most recent meeting, the committee advised on really the impact of patients on the growing number of precision medicine trials, what it's going to look like with

new trials that have a smaller number of patients, what that means to the community and what that's going to look like for individual patients.

They also advise the NCI's -- one of their specific programs that came out of the Cancer Moonshot's Blue Ribbon Panel that is looking at creating a rare tumor patient engagement network where patients will submit their data and then that will help -- they'll look at the data, and then that will help drive future clinical trials.

And so I just want to end on a thank you. You know, thank you again for having us. It's a pleasure to be here, and it's really an honor to work with advocates each and every day. In my year-plus working at OAR, I found advocates to be an incredibly dedicated and inspiring group. You know, while I'm not a cancer survivor myself, I am a liver transplant patient; I received one when I was 9 years old. So I feel very, very fortunate, that's for sure, and very indebted to advocates and to the FDA and just the community, the research community, as a whole.

So I will leave with one final thought, and I think that this is really what I -- there are, obviously, immeasurable reasons on why to include patient advocates in all the work we do, but I think, you know, one of the things I always come back to, it's an incredible leap of faith to participate in a clinical trial; it really is. It's just for a patient to put their hands in -- put their health in the hands of an investigator, and it's an incredibly courageous thing to do. And so I think that's one of the many reasons that we really strive to include patient advocates, really, in all of our work, but particularly in clinical trials, throughout the entire process.

So, again, I'll end on that note, and I just want to thank you all again for having me, and it's been a pleasure, and I look forward to the rest of the day. Thank you, all.

(Applause.)

MR. CONWAY: Thank you for your presentation and for your candor at the personal

level.

We'll now hear a presentation from Scripps Translational Institute.

MS. McCOLLISTER-SLIPP: Hi, there. It's such a pleasure to be here. I'm Anna McCollister-Slipp, and I have an affiliation with the Scripps Translational Science Institute as the Chief Advocate for Participatory Research. But I want to be clear that what I'm saying today represents my thoughts, my opinions, my perspective exclusively. And while there are some brilliant people at Scripps, I occasionally agree with them, often agree with everything they say. I just want to make sure that you know that I'm not speaking for them, I'm speaking from my perspective as a patient, as an advocate, as an entrepreneur who is committed to working to make research better and more effective.

So I also want to say that I am also one of you. I'm very much here because I'm a patient and an advocate and very much accidentally involved in a research enterprise. I have a background in journalism and public affairs and got frustrated as a patient who has a very complex Type 1 diabetes. I take lots of different medications, use lots of different devices, and felt like we needed to improve the research enterprise and structure to incorporate more patient-appropriate methods.

So that's how I kind of embarked on this. I am a member, also a patient advocate, on CDRH Advisory Committees. So, actually, Bray and I went through our training together a few years ago, and we're still involved, so it's a great group of people.

I want to start by telling you a little about a case study that I have or a situation I faced a little over a year ago as a member, a patient member of a CDRH Advisory Committee, and then I'll tell you a little bit about some of the stuff that I'm doing, along with my colleagues at Scripps and some other folks, to try to make the process a bit better from the research perspective.

So a little over a year ago I was a patient advocate who was asked to sit on an

Advisory Committee, which in the diabetes space really isn't that common. Just because of the nature of the way devices are approved and the 510(k) process, there just aren't that many Advisory Committees for diabetes devices. This happened to be an incredibly, incredibly important one, and I was really nervous about it for a variety of reasons.

The issue was a device was for continuous glucose monitor, these are monitors that give you your blood sugar level every 5 minutes. Incredibly important lifesaving technology. I use it diligently, always. Very, very important. The issue that we were trying to decide was whether or not the data that you get through this constant data stream that comes on your iPhone is accurate enough to be able to dose insulin. If you don't have diabetes, first of all, congratulations. But secondly, you probably don't realize that insulin is very easily a fatal drug. So if you dose it incorrectly, you could die, and people often do, often in the middle of the night, and these devices can alert you if you're getting too low into a dangerous level. So these are lifesaving devices.

Because of the way that the regulations are written, Medicare didn't cover them because you need another device to be able to calibrate your continuous glucose monitor. So the issue that we were trying to decide was whether or not this data was accurate enough to be able to dose insulin, but the real issue that was driving the submission for this new indication was the need for people to be able to still access these devices when they were aged into Medicare because their -- I know my physician had at least one patient who, because they aged into Medicare, they lost their CGM and they died from insulin, too much insulin. A really big issue. Many, many lives were at stake. We weren't allowed to talk necessarily about the fact that this was really about a Medicare reimbursement effort in, you know, the population, but that's ultimately what it was about. So we had to decide about the evidence that was presented to us in the data.

So a little bit about the company, a very active company, very engaged with the

community, the diabetes patient community. Really forward thinking in terms of working directly with patients and reaching out to patients. Very cognizant of the skills of the patients and the sophistication of the patient population, which is a very sophisticated patient population because of the nature of the disease and the fact that we live with data -- we really -- our devices and disease particularly well. So very engaged, very involved.

And the team at FDA is also incredibly brilliant, smart, interested in working with us. So you have a great team, important device, critical issue, super-dosed patient population, and these devices are constantly beaming data every 5 minutes to the cloud. The company collects real-world data, lots of real-world data for tens of thousands of patients.

So we have patients and the research and a brilliant FDA team, lots of real-world data, a critical issue, and I'm the only patient sitting on this advisory board. I have a background in data analytics as well, and the model that -- the evidence they present to us is not anecdotal. It's not anecdotal, which is fine, except this is not anecdotal data based on physiological parameters from healthy 20-year-old girls that was done by -- the measures were taken, I don't know, 10, 15 years ago, and they're trying to get these devices into clinical trials.

I'm sitting there as a patient who has microvascular complications, who isn't yet on Medicare but I'm older than 20, and I'm certainly not a male, and I know that there's a lot of real-world data out there and a lot of really smart patients who could contribute some ideas about how to come up with better studies, and I have about 10 just from reading it, and I'm looking at modeling, and I'm thinking why on earth is this where we are? Why don't we have a better process for getting patients involved in giving input into the regulatory decision-making process and the structure of research design? We have all the right materials, all the right audience, the right people, everybody, and we don't have a process.

So what I'm going to talk to you about today is my frustrations with this process, the

fact that we're not here, the fact that even given all of the scenarios that I just described, that we still have a process that creates modeling data when we could be doing so much better. We could be producing science that's way more relevant to the patients involved, to the audience of patients that are ultimately going to be served, and far more helpful and instructive to the regulatory process, and that's really the reimbursement process.

At the end of the day, for that particular Advisory Committee, the decision that was made was the correct one. The devices were approved, everybody ought to use it for dosing, everybody who was sitting on that panel already knew that, the Agency already knew that, but the data that were used to be able to make that decision -- and I was not -- as a patient member, I do not have a vote on the Committee, I'm just a consultant member of the Committee -- was the patients who came to the table who submitted testimony about how critical that this was. There were hundreds of patients who flew across the country to come to this exact room to tell the Agency how important it was. Any one of those patients, had they been consulted, could have come up with a better research design than what was presented.

So what we're doing with my colleagues at Scripps, and with support from Janssen Pharma Companies, we're creating a platform to make this process easier. We started a few years ago in coming up with a concept for a platform we're calling VitalCrowd, and the whole idea is to take some of the models that exist in other sectors of the economy and the consumer sector, the technology sector, to scientific enterprises like InnoCentive.com, where you're trying to break through the silos, trying to bring people together so that they can work together collaboratively to solve problems or through the app store where you're constantly in there making things better. But to take these models that we have from other sectors and to incorporate them into designing research that isn't just a focus group, it's not just a collection of people who happen to be available to be at a conference room in Des

Moines on a random Tuesday where an academic research center is located, but something that's a bit scalable and is able to reach people in their homes when it's convenient to them, but also brings them into the process.

So these are some of the models that we started with. This is the concept, it's really about making research better, making it more collaborative, putting patients and caregivers, community physicians, healthcare providers in the community on the same par to collaborate directly with researchers or regulators or sponsors of trials, to be able to interact directly to share ideas, to iterate on any of those ideas dynamically in a way that's respectful and where the contributions and the expertise of everybody involved is considered on an equal level.

On the one hand, you can see we've got what I call designers, patients, caregivers, advocates, etc. On the other side you've got sponsors, researchers, etc. And VitalCrowd will be the glue in the platform that brings them together in a way that's accessible for everybody.

There are a couple of different things that we're starting with in terms of making this happen. First is, we're beginning with protocol refinement, starting with the idea that a sponsor or a researcher has for a trial, making it available, exposing it in a way that's accessible to patients and caregivers, making it possible for them to give input in a way that's convenient for them, and then creating that connection between them and the researchers so that they can build on this idea and make it better.

In addition, we're also trying to create a way so that I and people like you and others that we all know from our respective patient communities can propose other research that makes sense to them, things that they know will be far more relevant than what they're seeing out there, whether it's related to a regulatory decision or a new drug or a device or just better understanding how to improve care, understanding the health of your

community. And, again, making it possible for -- you know, I, for whatever reason, had the audacity to be able to connect with researchers and to find people who are willing to work with me on these kinds of things. That's a much harder lift for a lot of people who don't happen to live in Washington, D.C., and don't happen to be able to meet and work with some of the people that I've had a chance to work with. There's a lot of really great people out there, I know you guys already know this, and we want to make it possible for them to participate in the process and to make suggestions of their own.

So we started with an alpha site. It's up right now on VitalCrowd.org. There are a lot of things about it that you can see that, I think, worked and worked well. There are a lot of things about it that didn't work particularly well at all. But we learned a lot from the process of putting it up there and exposing it to individuals and giving them the ability to see what it was, and what we saw was that even mobilized, really engaged, very smart patient populations still had issues with the way that we thought it would work. But we can make a lift as easy as possible, particularly if you're engaging in an online platform. Everybody has the attention span of a gnat, and it's shrinking every day, so we need to look at possible -- so that people can interact with what's given to them, and if it's meaningful and it's not patronizing, it doesn't speak down to them, but makes it possible for them to give valuable contributions that are digestible.

And then also, we really learned that what we thought would work, what I thought was brilliant, it was not that brilliant. And we've had a couple of good things about it, but for the most part, you learn a lot about what you really don't know, which is fine, and that's the whole process of tech development and platform development. It's a starting point and you learn as you go.

So with the support of the innovations team, which is part of Janssen Research and Development Operation Center, we're building a beta version of VitalCrowd. It's new, it's

improved, it's -- we've taken it out of the learnings that we have from the alpha version. We're building a beta version that's much more focused on user interactions, user interface, giving people what they need to be able to give constructive input and feedback and making it possible, doing it in a way that really respects and honors and builds the community as opposed to computer -- and supporting the advocacy groups that each of you represent and where we all come from and do it in a way that's respectful and fun, and to the extent to that you can gamify research design, we're doing that. We're still very early in the process. We're building a site, we're going to be doing two different beta tests with two different clinical trials that Janssen is working on, and you know, they're an incredible partner both in helping us figure out how to do this, how to make it usable at the researcher and sponsor side, as well as accessible for patients.

So, in summary, all of this stuff that we're talking about is incredibly important because it has an incredibly valuable role, not just for the Agency but for those of us in the patient community, all of whom live with the reality of research not done as well as it could be, as well as living with the reality and the promise of all of the incredible technology and tools and medications, etc., that are necessary for us to live and sustain a healthy life.

In terms of what we've learned so far, we know that this input needs to come in very early in the process, the earlier the better. Ideas come from patients that, you know, probably could get us there faster than some of the ideas that somebody who is a career researcher would have. Just because they don't live with the disease in the way that we do, they don't understand it at the level that we do. So the earlier we can involve individuals and patients in the process, the better. We need to make sure that the feedback is multifaceted, and it's not just about your symptoms and how you feel about something. There are people out there who have really good ideas about data, what kind of data is important and how to access that data and how to use it.

So I'm happy to answer any questions, but thank you so much, and again, congratulations to each of you for your roles on the Committee. And as a patient and an advocate, I'm really looking forward to seeing what you produce.

(Applause.)

MR. CONWAY: Thank you very much for your presentation and for sharing your background as a patient. I'd like to thank AstraZeneca, the National Cancer Institute, and Scripps Translational for their presentations.

At this point, we'll have Open Committee Discussion. As a reminder, although this portion is open to public observers, public attendees may not participate except at the specific request of the Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. Again, this helps the transcriptionist to identify the speakers for the transcript.

We'll have about 15 minutes for discussion, that's a reminder to committee members, and then we'll move into the second section of the agenda here. But for the speakers, as you come forward, again, if you could identify yourselves, and then I'll throw it over to the Committee here to ask any questions or have any conversation among ourselves, but our guests are here to ask questions.

MR. DUNLAP: I'm curious if our friend from AstraZeneca could comment on whether, after going through this process of mock testing the clinical process, if the actual study had what they were, if they did have a better measurable participation or retention outcomes than your normal process.

MS. O'BRIEN: Yes. Faye O'Brien, AstraZeneca.

Yes, the lupus trials are still ongoing. The last patient in -- has been reached, and we have exceeded our enrollment, retention, and compliance goals to date. And is it specific? It is in improvements and exceeding expectations. Is it because of the simulation? We

cannot draw a direct parallel and correlation, but certainly it is a contributing component of that. So yes, we have exceeded enrollment and retention rates with our studies.

MR. DUNLAP: And when you say exceeded, is it just a little exceeded or way exceeded, or can you put -- I'm pushing you for a metric you may not have, but do you have any feel for that?

MS. O'BRIEN: So the problem with the other two sponsors, in terms of they failed the global Phase III trials, was mostly around untimely recruitment and the retention component of it. And I would say that from a recruitment perspective, perhaps around 10 to 15% in terms of reduction in the time frame. I don't have the metrics associated with the retention today.

MR. CONWAY: Dr. Blackburne.

DR. BLACKBURNE: Yes. And, Ms. O'Brien, this question will be for you. It's kind of catchy. Rose Blackburne, and I'm the Industry Representative. I had a couple of questions.

One was around the simulation and the lupus. I work on lupus programs myself, so I know it's challenging because of the nature of the disease. So I was intrigued by your -- how you all immediately identified that you needed more African-American women patients because that's a challenge. So besides adding the Grady site -- and I'm familiar with Grady from training, so spot on. But besides just adding the site, what else did you do with the site to recruit the patients, specifically? Because that's always a challenge in different indications as well. What, you know, outreach within Grady or the Grady community --

MS. O'BRIEN: Right.

DR. BLACKBURNE: -- did you do to --

MS. O'BRIEN: So we've been fortunate enough to have a very active, passionate investigator PI from the school of medicine here, Dr. Lin (ph.), who personally recruited the patients, this was from a pool of his patients, and he was able to recruit the patients to

participate in this over a week period, so it wasn't very difficult. With the nature of -- the interviewers were African American to facilitate the discussion, open dialogue.

And also the manuscript that we published, we actually noted considerable differences between patient preferences between African-American patients and then the broad population in Pennsylvania. So, actually, the manuscript highlights what was in commonality in terms of recommendations and what were the variances in terms of that. And it really highlights that, as it was mentioned, just the ad hoc interview of random patients available at a given time. This will give you that proper view of the totality of the patient population.

So considerable effort was made to recruit African Americans, to make sure that they're comfortable, the trust element in terms of the interview process, and thorough analysis of the variances by demographic background.

DR. BLACKBURNE: And a basic question, and this comes up in studies, and some sites are more successful at it. Did you ask or is it in general a question that you ask sites about office hours for study patients? Because that would eliminate a lot of barriers, you know, everybody in the room works or has -- you know, if you're going as a patient or with a patient, office hours for care is a huge barrier. So was that addressed, not specifically with the simulation, but in general? And how you identify investigators, is that something to ask them? Are they willing to have extended hours outside of 9:00 to 5:00?

MS. O'BRIEN: Absolutely. So what we're doing, actually, at post-simulation, what we learned was that we really need to be sensitive to the demographics in terms of working population, adolescents with school hours, let's say --

DR. BLACKBURNE: Parents.

MS. O'BRIEN: -- holiday, receiving the summer.

DR. BLACKBURNE: Yeah.

MS. O'BRIEN: Be sensitive to the climate. In Atlanta, it gets really hot, and use of the public transportation is actually better to get to the office visits. So these are some of the subtleties that we learned during the simulations and the nature that we are actually proactively addressing that with the sites, for example, making sure that we're adequately reimbursing sites for having evening and weekend hours. So to actually hear that from the patients and take it back internally to the teams is very powerful because it's an evidence-based recommendation.

DR. BLACKBURNE: Thank you.

MS. O'BRIEN: You're welcome.

MR. CONWAY: Great, we're going to move into a quick-fire round here. So we'll move to Cynthia, then go to Dr. Seelman, Amye, and we'll end with Mr. Downs. Okay.

MS. CHAUHAN: This is for you.

MS. O'BRIEN: Got you.

MS. CHAUHAN: Cynthia Chauhan. I appreciate the efforts you are making. I do have a concern, if I was hearing you correctly, and that is you are still maintaining distance between the researchers and the patients. The patients are not being involved in the actual development of the concept and interacting directly with the researchers and I'm interested in that.

MS. O'BRIEN: No, sure. And of course, that's a valid concern. So simulation and use of the online social communities is just two of the tools that we use in terms of soliciting patient feedback, and I highlighted them today only because they're more novel and new in nature. We engage patient associations, advocacy groups, patient panels throughout our development process from the very early on when we're putting together a target product profile. So we do have direct, active engagement with the patients from the concept to the finalization of our protocol. I just highlighted two of those mechanisms today.

MS. CHAUHAN: Direct with the researchers?

MS. O'BRIEN: Yes. So we have patient advisory panels that we invite when we are initially assessing the unmet patient need before we have -- before we even go into a Phase I study. Yes. And that's really a typical practice within pharma.

MR. CONWAY: Great. Dr. Seelman.

DR. SEELMAN: Kate Seelman.

I believe it was you, but I'm inviting any one of the three of you to respond to this one. In terms of returns on investment metrics, what are some of the emerging concepts, factors, values, that might be measured, and how can consumers be involved in the development of the metrics?

MS. O'BRIEN: So specifically, in my talk, I mentioned actually obtaining feedback from the patient, and there's an instrument called PAM, Patient Activation Measurement, that's typically used in a clinical setting, where it's just a 13-item scale that measures patients' knowledge and confidence in their disease and treatment. So it's an instrument that's used widely within the organization, and we're adopting it internally within AstraZeneca to measure the effectiveness of our patient-centric initiatives. So the instrument is called PAM, Patient Activation Measurement. Of course, you know, we have traditional ways of comparing recruitment rates, retention rates, compliance factors, expected versus actually achieved based on implementation of patient-centric initiatives as well.

MR. CONWAY: Great.

MS. O'BRIEN: I will mention one other component. In reality, most of these initiatives are not cost prohibitive; they're not very expensive.

MR. CONWAY: Great, thank you.

Amye.

MS. LEONG: Amye Leong. Thank you very much.

My question is for all three of you, so you might as well stay up there. First of all, I want to thank each of you for very interesting presentations, getting down to the nuts and bolts, if you will, of how you do it and how you strategically look at this, and then how you incrementally begin to input and learn from it. That learning system site is very, very critical for everybody in this room to hear about.

What I'm interested in is, just as you alluded to, actually, I know we're not supposed to be talking about cost, so let's talk about effort and value. I would love to hear from each of you, at your various stages of development, in industry, in patient-led industry collaborations, in the NCI perspective. Given the amount of effort, so the percent of change, if you will, to move to the state that you are currently in now, because that's all we can deal with is what is now, what has been the reaction among your peers and/or your industry with this effort and has that outcome, to you, been of value?

And we're also talking about the aspect of time. Does patient engagement extend a time frame in each of your scenarios? How have you had to deal with that? How has that impacted the value of what it is that you're doing? So I'd appreciate that. And if there were any barriers to that. I know it's a loaded question in many ways, but pick any part of that you'd like to address. Thank you.

MS. McCOLLISTER-SLIPP: I think these are excellent questions, and I'm not sure I have a satisfactory answer to them, other than to say that part of what we're hoping to accomplish with VitalCrowd is to decrease the amount of time and effort on everybody's part, I mean, because it's really difficult for whether it's a pharma or a device company or a regulatory agency to put the process in place to make this stuff happen. Even if you go with the more sort of analog ways of doing it that we're all familiar with from, you know, focus groups or multiple focus groups or advisory committees or whatever, the nature of how

those things work makes it really difficult to do it quickly and iteratively.

I'll say that we aren't there yet because we're just building the beta version of this site, which I don't know if any of you have ever built anything with technology, it takes way longer than whatever you thought it was going to take when you started, even though you tried to pretend that you knew that it was going to take a long time. So it's very much a process, but you know, our plan is that once we get the site built, we can -- the way they're designing it, so we'll be able to build it and iterate it out much more quickly than what has been so far.

So the things that you've mentioned are real barriers for everybody involved, whether it's the patients, which is the perspective that I'm coming from, whether it's the -- you know, anybody involved. I mean, the amount of risk involved for a company submitting something to FDA is significant, so you know, there is a lot of pressures on the part of, you know, the sponsors of various things that make it much easier to not do this than to do it. So there's a lot of real commitment on the part of -- certainly, the people I'm working with at Janssen, to try to make this work and then make it happen. So I don't know if I've answered any of your questions.

MS. LEONG: You have.

MS. McCOLLISTER-SLIPP: But that's sort of where we are.

MS. LEONG: Thank you.

MR. FREIMUTH: John Freimuth with NCI. You know, we talk a lot about engaging the right advocate for the right activity at the right time, and I think that that's something that we are constantly learning more and more about and I think that, you know, when we -- when we're able to do that, it does, you know, help a lot of time frames, whether it's having that patient perspective included very early on will help with the timing for accrual for a study. But I think that, you know, we are always looking at improving.

You know, one thing that I know I've heard specifically for the National Clinical Trials Network is that, you know, PIs could be expressing a little bit of frustration that they were hearing advocate feedback a little bit later on in the process. So okay, let's involve them early on rather than have this back-and-forth about whether it's an informed consent form or a concept. You know, if they're engageable right at the get-go, then, you know, it will work a little bit more seamlessly and you'll get that feedback very early on and be able to carry that through.

And, again, it's not always about things like accrual or that sort of thing, but I think that that is something very much to be considered and, you know, we all want studies that do accrual and that help patient outcomes, and I think that, you know, including patients really early on at that right time can really make for a much more streamlined and efficient process. I hope that answers your question. If not, I'm happy to talk afterwards.

MS. LEONG: Thank you.

MS. O'BRIEN: The level of effort is significant. AstraZeneca is a 60,000-person organization, and several years back, about 5 years back, we decided that it's a culture change and it requires dedicated people, it requires ambassadors internally within AstraZeneca. It requires connecting with the teams at the execution level to convince them why investment in patient-centricity measures will pay off, and it does pay off. It means one or two shaved off from the clinical trials is in the millions in terms of the cost reduction.

And frankly, you know, it is a shame to lose out on the opportunity that, now that pharma can connect directly from the patients and it's normal, we're just limited to input from the sites, to hear about the patients and what they want is a tremendous opportunity for improvement, and that's something that AstraZeneca didn't want to walk away from, so therefore they involve the leaders in the field, but the investment and the time perspective is significant.

MS. LEONG: I appreciate all your responses. Thank you very much.

MR. CONWAY: Thank you.

We'll go to Mr. Downs now, and then we'll go to Dr. Parker, and we'll end out on this session with Suzie. Go ahead.

MR. DOWNS: Fred Downs.

The question is directed to all three of you, not for an answer now, but do you have lessons learned, and if you do, could you provide them to this group? Yes? No? Just say yes.

(Laughter.)

MR. DOWNS: Okay.

MR. CONWAY: I have a feeling that Mr. Downs is going to be a pretty interesting person on this Committee.

(Laughter.)

MR. CONWAY: Dr. Parker.

DR. PARKER: My question has to do with representation of underrepresented groups. AstraZeneca spoke specifically to the issue of recruiting African-American women, and lupus is something that affects African-American women rather significantly, but the site that you chose was Grady, and Grady is sort of like a catchment hospital for people who are, let's say, maybe financially or insurance deficient, and I think that sometimes when you start looking for underrepresented populations, that may not be the fairest representation.

So for each of you, we talk about patient advocacy groups, you talk about a platform. How are we making these innovations, if you will, or the input of these underrepresented groups, how are you seeking out these populations, and where are you seeking them out from?

MR. CONWAY: So, again, for the transcriptionist, as you come up, go ahead and

identify yourself.

MS. O'BRIEN: Faye O'Brien, AstraZeneca.

So in our lupus program, when we started conducting -- actually, implementing the Phase III program, we became sponsors of the Lupus Foundation of America, and at the central office, as well as local community, to make sure that we have that proper input in terms of feedback. Originally, Atlanta is actually one of the local chapters that we endorsed. We also make sure that in selecting the clinical sites, we have appropriate representation of sites that have access to minority patients. So that's a concerted effort, so when we conduct feasibility for site selection, we specifically inquire about the available patient population in the selected groups that are representative.

So in terms of inclusion of patients that need to come into an actual clinical trial, there are various mechanisms, that we make sure that we're casting the broadest net in terms of patient awareness about the clinical trial.

The mock visits, it's just a snapshot into what a patient experience could be going through the trials, and for obvious reasons, we could not include hundreds of patients in that exercise, so it was just a snapshot in terms of getting that initial feedback, given that this was a new area, therapeutic area, for AstraZeneca. But we are aware of the limitations in terms of how much we can generalize that data to the broader population, including the African-American population.

DR. PARKER: Well, there are other underrepresented groups, like Latinos, immigrants, and Atlanta is one of those populations or communities where we have a very large immigrant population that doesn't necessarily come to, let's say, a catchment hospital. That's all.

MS. O'BRIEN: No, we appreciate that. So yes, Grady Hospital is mostly under-insured and uninsured patient population that goes there. So clearly, that's something that,

in terms of obtaining that broader view, let's say patients, like me, that -- with the broader patient population that we get out to. We have a number of mechanisms to receive feedback. This was just one of the methods that we employed in terms of getting that -- obtaining that information.

I do want to mention this. You know, it was a pretty tough endeavor to get approval for the simulation, only because you're prolonging the finalization of the protocol by 2, 3 months just to get the input from these 12 patients. This was a major undertaking that took several months, and meanwhile, here is a team that just wants to go and get the first patient in, right? So it took us about 3 months to conduct the simulation, but it was definitely well worth it in terms of the learnings.

MR. CONWAY: Anyone else who would like to respond to Dr. Parker?

MS. McCOLLISTER-SLIPP: Again, I'm happy to take a stab, but I don't know how satisfactory my response will be, in part, because we're just building the beta version, so we're really just getting started. By the very nature of what we're building, it's an online platform, so you know -- everybody will say, well, my mother isn't really doing an online thing here. They'll come up with anecdotes about that.

But the reality is, is if you start looking at the data around how people interact and how they use platforms, the gender divide is decreasing. It isn't perfect, and I'll pretend that that's, you know, going to be the be-all/end-all for every possible underrepresented population, but it's a start. And it's certainly far more representative than, you know, some of the tools that we currently have at our disposal. So that's very much a part of what we want to address, is to create something that will be accessible to people, whether you define underrepresented based on ethnicity or age or disability. So we think that the approach we're taking will make it possible, easier for a diverse group, however you define diversity, to be able to participate in the design of research.

So that's our goal and we're early. I'll be happy to show you where we are as we develop and, you know, engage with you guys as this process unfolds, but that's certainly one of our goals. You know, not just to tip a box, but because, based on my personal experience interacting with other advocates, I know that there are a lot of really smart, insightful people who don't manage to make it to, you know, the Hilton in Gaithersburg to be in the room with you guys. So that's really some kind of whatever it is we want to accomplish.

MR. CONWAY: Great, thank you.

Go ahead.

MR. FREIMUTH: Yeah, thank you for your question. And, you know, I can speak to, you know, the way in which we are working with underrepresented populations within advocates. You know, we have a network of over 200 active advocates that we call upon for different activities throughout the NCI, and we are currently in the development of a recruitment plan to kind of increase, you know, some of these populations that you mentioned, and I think we have some representation, but we want to always make sure that if people -- you know, that we get that feedback from all the different groups, whether it's the African-American population, Latino communities or also -- I know one that's talked about quite a bit is rural populations that might not have access to a cancer center nearby. You know, places in Appalachia, those sorts of different communities.

So I think that it's, you know, fun, and from our OARs, advocacy relations network, it's something that we -- you know, we obviously, you know, make sure that we have our presentation on our National Council of Research Advocates as well as throughout some of these other initiatives on our patient advocate steering committee. But I think, you know, that is something that we will always look at since it is always changing a little bit and make sure that we are -- that the patient input is representing all different -- the different

communities, especially those that historically have been underrepresented. So I hope that answers your question. And I'd be happy to talk after. So thank you.

MR. CONWAY: Great, thank you very much.

Suz.

MS. SCHRANDT: Hi, Suz Schrandt.

And this question is for Faye. Sorry, Faye, the last time you have to get up. Thank you for sharing the case study that you shared. My question was about the continuity. So, you know, in the spirit of true engagement, is relational and not transactional -- I think it was very clear that there was continuous engagement with the people who were involved in the trial, so like a lot of effort to make them feel valued, feel heard, and really be treated as whole people. My question is specific to the patient advisory board. You mentioned their involvement up front, but I don't like the term "burden of disease," but helping to capture burden of disease and really think about sort of a target for treatment. Were they continuously involved, and was it an iterative process from start to finish, or was it more sort of did it end at the front end?

MS. O'BRIEN: Right. So, in general, AstraZeneca is focused in a limited number of therapeutic areas and because they deal in each of those, you know, diseases within that therapeutic area. We do have patient advisory boards that are consistent and throughout the development of a compound or a cross-compound, let's say, for asthma, so we do have that continuity. And we're also tapping to ad hoc patient advisory boards and especially when we are going into new countries where we need to obtain country-specific insights. So the answer is all the above, continuous engagement of patient advisory boards and different advisory boards, depending on the situation.

MS. SCHRANDT: So, for example, if you wanted to make a clinical trial protocol revision midway through, would that be something you would take to the patient advisory

board for input? I'm trying to get a sense for, real technically, what that looks like just as a roadmap for others.

MS. O'BRIEN: I can't speak to all the programs that AstraZeneca has specifically for our lupus program. We have a scientific steering committee that has been in force for about 6 years now, so they've been ushering this. So all protocol changes or major shifts to a development plan requires approval from the steering committee meeting. To my knowledge, we don't have a patient member in that steering committee, but we do tap into various patient inputs throughout the study for us to come up with an idea of changing the course of the studies. Yeah, sure.

MR. CONWAY: Great, thank you very much.

At this point, we're going to go ahead and move into a second topic, which is Patient Recruitment, Enrolment, and Retention, and we'll hear a presentation from Johnson & Johnson.

MS. FELICIONE: Good morning, everybody. And thank you, Chairman Conway and the Committee, for inviting us to be here today. We wanted to -- and also thinking about building, it was a good segue from the previous presentation. What we're going to share is something that is somewhat similar, it's also a clinical trial simulation, but hopefully this gives the opportunity to share something that was done in medical devices with a combination product.

My name is Elise Felicione, and I'm with Johnson & Johnson. I'm going to be co-presenter today with Amy Loescher. I will kick things off and then turn things over to Amy, and then I will make some concluding remarks.

Let's see. Okay, good. So in Johnson & Johnson, we recognize the case for patient-centered trial design. Over the past 5 years we've had many conversations with patients and with advocates who really understand how things are transforming when it comes to

medicines and product development based on the changing role of patients. So as with many organizations, we have synthesized that changing role in a way that we can communicate it well, internally and externally.

So when we look at patients, this is based on the patient is picking up more of the direct cost of healthcare, becoming more of a sub-advocate and taking their healthcare into their own personal hands and those of their care circle and their family, becoming -- having more of a voice and really being a research partner versus a participant or a subject and therefore having more influence in research. And then as an influencer, this meeting today pretty much describes that role.

So where we want to be: We continue to create products and medicines for patients, but we're moving into a role where we want to create products and medicines with patients. So patient-centered trial design is what we needed to do, but this was -- I think Dr. Tarver characterized this well in doing the recap from the round table yesterday about, you know, the question is how do we do that? How do we ask patients? First of all, find the patients and then engage with them, listen to what they have to say, and then how do we translate that feedback into actionable insights that we can then take and help to influence how we plan our clinical development strategy, how we design our clinical trials, and even once the trial is designed, implement those trials, collect continuous feedback throughout the life cycle and apply that so that we improve that experience all around.

What we did is we -- very similar to AstraZeneca, we tested a few different methodologies where we could, yeah, get -- conduct patient-centered trial design. We wanted to test methods that moved a little bit beyond the focus group. There was a lot of discussion about diversity and, you know, patients. This is a very heterogeneous term, really, and we wanted to see how we could capture more of an aggregate voice, look at some methods that were quantitative, qualitative, at different time points in that

development life cycle. We tested many methods around actual trial design, and some of the more novel methods, we're partnering, as Anna McCollister-Slipp mentioned, on -- you know, even at the ideation phase, how do we get patients at the white board together with the researchers and co-create that research study?

The case study that we want to share today is a simulation, and what we -- this was thinking about okay, we need to test the usability of the study. Oftentimes, if something doesn't work end to end with the different workflows among the investigator, the coordinator, the participant, the caregiver, we only maybe know that once the trial has started and we learn that maybe a little bit too late. We wanted to put a prototype of all of those processes into a simulation environment and really road test it and see what worked, what didn't, in an effort to -- again, it was very well said, to augment those things that make it better for the participant and minimize the burdens.

With that, I want to turn things over to Amy, and she'll tell you a little bit more about the trial and about the process that we used for simulation.

MS. LOESCHER: Thank you. And I want to thank everybody, as well, for inviting us here today. My name is Amy Loescher and I'm at Johnson & Johnson.

Okay, so it's really important to understand, before we go into the simulation, the trial at a high level in the patient population that we were recruiting into this trial. This is a Phase II trial in age-related macular degeneration, and for those of you who aren't or are aware, it's a very devastating degenerative disease which accounts for about 2 million -- well, there's about 2 million cases in the U.S. alone of these patients and accounts for the majority of severe vision loss in people over the age of 50. There is also no known cure or treatment, so a very unmet medical need here. And the patients that we were recruiting into this trial were between the ages of 55 to 90 years old, and in reality, the average age that we ended up recruiting was 77. So that plays a big, you know, factor into this

particular elderly patient population.

Okay, so how did we do this? Again, as Elise said, it's kind of the same concept, different flavor, from what AstraZeneca did. As in any kind of pilot that you do, the biggest part is the preparation. So we worked very closely with our partners at Healthy Eyes, and the first thing we did is identified our objectives and what we wanted to get out of this. And it was very simple; we wanted to, to the best of our ability, simulate a patient experience going through one of our more time-intensive study visits, collect their feedback, collect patient feedback, and then try to use it to, you know, make the participant experience much better so that patients would want to enroll in our study and stay in our study.

So what you see here is actually a copy -- a picture of our clinic that we set up, right? So we had to set up this mock clinic. This was done in a market research facility, actually in Alexandria, and every single piece of equipment was rented and set up, and we actually spent some time moving this around so that the flow looked good. And then we had to find the patients to participate in the study.

So the patients were obtained through an opt-in consumer database, and they had to meet a couple criteria. They had to agree to bring in their caregiver, and they had to have a diagnosis of age-related macular degeneration, and they had to agree to spend 3 hours with us. And when I say "with us," it was actually you had two investigators that were actually ophthalmologists, and a study coordinator that was actually familiar with ophthalmology studies as well. They actually took the patients through the experience. And we were behind -- this is what we saw behind a single-glass observation area in this market research facility. We were behind there watching all the interactions, as well as the -- and I'll tell you a little bit more about that -- the president from the electronic informed consent company, because we did use an electronic informed consent in this trial, and that

was another key part of our learnings we wanted to get at, was the use of that.

So how did we do this? We had a very specific plan as to what we wanted that 3 hours to look like for the patients, and the first thing we did is we sat them in front of this Candy Land-looking map, which is perfect because it tells, you know, this is where you're going to be, you know, this is how long you're going to be, and this is what's going to happen at every visit. And just for information, this was a single-dose study with a 5-year follow-up with an investigational cell therapy given by an investigational device in a very specialized surgical procedure. So this seemed to resonate with the patients, and they had a lot of questions; they would stand up there and point and go okay, well, what does that mean and what does that abbreviation mean, because, you know, we tend to be very acronym-centric in our business. So it was a very good learning tool.

So after they did that and they understood the trial, then we sat them down with our electronic informed consent, which is basically, as most of you know, a consent form on a tablet where you can swipe when you've read a page and you can select definitions for words that, you know, you want to know more about.

And then we actually took them through the instrumentation that you see, that you saw in the last slide, and we said, okay, now you're -- we tried to simulate the screening visit, which we thought was going to be 5 hours long, but actually it turned into -- and I'll get into that later. So we took them through each piece of instrumentation, and we said okay, now you go through this and this is going to take 40 minutes, and then you're going to go through this, and this would take 30 minutes. You know, it's various imaging, photo machines and, you know, eye tests, some PROs and things like that.

And then after we did all of that, we brought them back and we said, okay, what kind of questions do you have? And they asked a lot of questions and what you see here is a gentleman who -- you know, he was actually -- he had to pull out his magnifying glass to

read our electronic informed consent. So we got their feedback, we collated it, and you know, obviously just kind of took it all in. And then we got, like, a testimonial from each of the patients on their disease and the effects of the disease on their day-to-day living.

So what did we learn and what changes did we make? So the first thing we did, we heard very loud and clear is, these are elderly patients. They don't like to be driving around going to different places, finding the parking, getting to the site, getting to the OR, which may be at a different location on the site. You know, we had these in a lot of major medical institutions -- Chicago, Philly -- and we all know how easy it is to get around those cities and with parking and things like that. So we actually employed a very nice door-to-door car service where they would go and pick up the patients and their caregivers, if they wanted to come along -- or if they didn't, then they didn't have to -- and bring them to the door of the clinic or the hospital or whatever. And then if needed, the coordinators could go down and get them at the front door and bring them up, right, because often that's part of the process as well, is finding out where you have to be.

We also provided hotel service for the night before surgery. So for these kind of surgeries, these types of conditions, are very early in the morning, sometimes 7:00 a.m. So, again, it's hard to get into Philly and, you know, by 7:00 a.m. find parking and then get up to where you need to be. And by far, this was the biggest thing that we could've done and the best feedback that we received was this car service and just really taking care to, you know, make the patients' lives a lot easier.

The second thing we learned a lot about was our electronic informed consent. I mean, this is really -- it's getting more and more adoption, but we thought that this would be the best thing for these patients because -- right, because they can make the font bigger, it had an audio readout and, you know, it's just easier to use, we thought. But what happened is, when we sat these tablets in front of these patients, they were sneering, and

they couldn't read them, and they couldn't differentiate color, like green meant swipe to the next page. And so we had to make some modifications there; we had to provide large-screen monitors for our sites, you know, so they were clean and so that they could just have a very, very big font. And some of the patients also did not feel comfortable with the technology. They put up with it. So they had to have the study coordinator and, actually, in the simulation, they had to, you know, kind of help them swipe and read through. We also provided copies of the paper in very large font because some people just would prefer that.

Oh, another thing we did is the informed consent. We had a lot of questions during the interviews about how does the product -- how is it delivered to the back of the eye with the device? Lots of confusion about that. So we actually took a little, like, cartoon video that we had made, and we embedded that into the informed consent, so you could, like, hit a button and you could see how the product was, you know, delivered and what that looked like.

And then finally, we also -- as I said earlier, we thought that our screening visit would be 5 hours. In reality, it was 8 and it was late, and these patients, if you watched them during the simulation, they got tired and they -- you know, they'd ask for breaks, and they'd ask for, you know, water or they'd ask for -- you know, I just need to take a breather. So we actually ended up implementing this visit schedule for a screening visit, and that was what we heard from the sites as well, is that, you know, these guys just can't -- they were falling asleep in our instrumentation. You know, they were just tired. And so that seemed to be very, very helpful.

What they told us is, they said, you know, we don't mind sitting at a clinic for, you know, 6, 7, 8 hours, but can you just please let me know so I can bring what I want, you know, to keep myself busy, whether it's my Kindle or whatever? And so we developed some very nice cards that said, okay, at Visit 4 you're going to be expected to be here for 3

hours, and this is what's going to happen at that visit, and they seemed to be very appreciative of that.

And then, finally, I think -- and this is such basic common sense and this can be applied to any single clinical trial we do -- soft skills. The investigator and the study coordinator that did this simulation were so engaging and so lovely, and they were just, you know, kind of flirtatious with the patients, and they seemed to like that. So I think, you know, what the patients told us was, you know, if everybody -- if I could be treated like this all the time, I'd have no problem coming in and being part of your trial. So, you know, just being nice to people and you know, just being engaging and listening to them.

And the other thing is just what they told us, they said, "And also, can you give us a comfortable chair, Wi-Fi would be great, water and a snack is also awesome." So we actually had to -- we had a secondary investigator meeting, and we trained all of our investigative sites on these soft skills, and we said, hey, look, we know that this seems really obvious, but can you just, you know, be nice to people and let them know how much -- you know, how long they're going to have to be there and just provide some water and some granola bars or something like that? And I have to say the net result was, at 6 months post-enrollment of our last patient, we had zero dropouts, which is highly unusual. So I think it was very, very successful.

So I think that's what I had. I'm going to send Elise back up for closing remarks.

MS. FELICIONE: So I see I'm looking at the red light on the timer, and we're over time a bit. Just to close things, this case study was representative of just, you know, one step. We wanted to see how this would work, and for all us that participated and looked across a two-way mirror, it was very inspirational, and we thought oh, my gosh, absolutely, we should do this all the time.

In order to motivate, you know, and inspire the rest of our organization, we created

a documentary video. If we have time, we can show it; it's probably just 1 minute in length. So --

MR. CONWAY: Sorry, we'll be going on to the next speaker.

MS. FELICIONE: Oh, we will? Okay. Thank you.

MR. CONWAY: Great. Our next presentation is by Boston Scientific.

DR. STEIN: Great. Well, good morning. Thank you. I'm Ken Stein. I'm the Chief Medical Officer for the Rhythm Management Group and for Global Health Policy at Boston Scientific. I want to thank the Committee. I'm really gratified and quite humbled to have been asked to be here to speak to all of you. You know, I should say, in addition to my role at Boston Scientific, I'm on scientific advisory boards for OptumLabs and for IBM Watson for life sciences, and to continue a theme, and probably relevant here, I'm also a patient with high blood cholesterol and with atrial fibrillation.

What I want to speak to you today specifically about the issue of better patient engagement, enrollment, and retention in trials is to cover, first of all, a couple of different initiatives that we've developed around enrolling more representative populations in our trials. I want to speak both to an initiative called WIN-Her, which is designed to improve the enrollment of female subjects into cardiovascular clinical trials -- that's been a huge miss in our disease space -- as well as the Platinum Diversity trial, which was aimed more broadly at increasing enrollment of underrepresented populations in cardiovascular device trials, specifically with cardiac stents. Then also, I'll come back and revisit a topic from this morning, which is involving patients very directly in the design and continued execution of our trials by including a patient representative as a full voting member on our trial steering committees.

I'll begin by talking about our WIN-Her Initiative. And before I speak directly about the initiative, I do want to acknowledge and thank FDA and CDRH for their collaboration

with us, and particularly Ms. O'Callaghan, who worked very closely with us in developing this initiative.

WIN-Her was designed, first, to improve our understanding of what have been the barriers that have prevented us from enrolling a sufficient number of women in cardiovascular clinical trials, and then having developed that understanding, to develop and test new enrollment approaches. And we are testing this initiative now in two recently initiated clinical trials, and a commitment to publish and share, very broadly with the community, what we learn from this effort. How did we do it? The initiative began with a series of interviews, focus groups, with patients and with physicians who've been enrolling patients into clinical trials, and then also a larger-scale, broad survey sent out to females with cardiovascular disease. Based on that, we developed new materials, and I'll share some of those findings and some of the materials with you, but also we found one of the learnings is people will focus on what you focus on with them. And so one of the key things has really just been the acknowledgement that we need to keep our clinical trial sites focused on enrolling a representative number of women in our trials.

So the questions that we asked were, to begin, are there different approaches that resonate better with women who are eligible for our trials? How do we design an effective pilot to test these approaches? What new materials and new processes do we need if we're going to solve or at least improve our approach to this problem? What's the best way to engage clinical sites? And what data is important for us to evaluate the success or the failure of this approach?

We're testing this, as I said, in two ongoing clinical trials. They've both recently started, so I can't tell you yet lessons learned and whether any of this is going to be a success or not, but I can tell you, there is one trial within the area of stroke prevention and atrial fibrillation, a second trial within the area of prevention of sudden cardiac arrest and

sudden cardiac death. We're only piloting these in the United States, although both of these are global trials. Part of that, frankly, is just resource limitations. Part of that is that the lessons that apply in the United States may not necessarily also apply in other geographies, and we do expect having to adapt whatever we learn in the United States to our international sites.

What we've developed have been both new patient-facing materials and an approach to a general trial brochure. One of the things that we learned is that a lot of people really do not go into this with a good understanding of research and clinical trials to begin with. What does it mean to be involved in a clinical trial? And, in fact, improving our materials not only aimed at women, but improving our materials aimed at everyone as a potential participant in a trial, but then also supplemental brochures specifically targeting women, a detailed patient website that says we are looking for women to enroll in this trial and why we need that, and a detailed questionnaire for patients. And by asking to have it filled out even by patients who then decline participation in a trial so we can understand what were the factors that led them to opt out of this research endeavor.

And I think this resonates a little bit with what we heard earlier just in terms of what we call the soft side, but it's a very important side, is developing suggested talking points for physicians and coordinators, a patient outreach letter, letters to be sent to referring physicians. The investigators in our trial are typically highly specialized proceduralists. They're not who our patients go to with a lot of their questions. And so gauging general practitioners, family practitioners in the research endeavor, we believe, is going to be very important.

And also developing follow-up guides for our coordinators: Again, this came up earlier, but it's a point that bears repeating. We need to give people more time to evaluate whether or not they want to participate in a trial. It just doesn't work well, you know, to

give them the 20-page consent form and say sign here or you're not going to be in the trial. And so go over that with our coordinators in creating a systemic way for them to send patients home with materials and then follow up after an adequate interval, we hope, is going to be important and is going to lead to success.

We are keeping, as I said, a screening log that will track how people made decisions, whether any of these materials resonated with patients, what are the factors that actually led patients to decline to participate in either of these two clinical trials. And as we go on through the trial, we are tracking enrollment to see whether we meet our goal, and if it's not, have a defined set of mitigating maneuvers.

So, again, the hope is that enhanced patient/physician-facing materials will help address what are discovered to be known barriers to enrollment of all subjects, but of women in particular. Education and training related to those enrollment barriers, we believe, will be critical. We are targeting enrollment of at least 40% women into the trial. We'd be delighted if it was 50%. And, again, we do plan to share whatever learnings we have from this widely and hope that it will inform future protocol design and protocol execution.

I want to turn to another trial. This was a trial that was recently completed. It's called the Platinum Diversity Trial. Again, as I said earlier, we know that women have been underrepresented in cardiovascular device trials. The same goes true for minority populations, African Americans, Latinos, etc. And what we decided to do with this trial was to run a trial that would only enroll patients from underrepresented populations. And, again, it gets back to what I said earlier about focus, asking sites to specifically focus on enrollment of populations where we have a more limited evidence base because of under-enrollment in our prior trials.

This trial enrolled 1,500 patients at 55 sites across the United States. The two

principal investigators, Dr. Batchelor at Florida State and Roxana Mehran at Mount Sinai Hospital -- and I would state that one of the things, again, that we hope will help is to have -- make sure that not all of our principal investigators and not all of our steering committee members look like me, but we also want to have more representation and more diversity among the folks who run our clinical trials.

This is a first-of-its-kind study that focused only on enrollment of women and minorities with coronary stents. And I'll begin with the end, the upshot, because here's one where I can tell you what we learned, and what we actually learned is this trial was much easier to execute than we had expected going in, you know, that the barriers to getting these underrepresented populations in our trials are not only not insurmountable, they're not as bad as we thought they were. And by focusing on this task, we were actually able to complete enrollment in this trial 6 full months ahead of schedule. And, again, for those of you who have had experience with clinical trials, 6 months may not sound like a lot; 6 months is close to miraculous in the space where I work.

How did we do it? Again, how did we pick our sites, and how did we manage the success? Part of it included engagement from the outset with our strategic partners. We do have a group called Close the Gap that's aimed specifically at reducing disparities and access to care and provision of care in the health system in the United States. So we reached out to the ABC, the Association of Black Cardiologists, to WomenHeart; include the Society for Cardiac Angiography and Intervention - Women in Innovation group; include National Medical Association, etc. Picked sites specifically based on their ability to serve and to enroll a diverse patient population. We did that both based on what we've known about those sites for our own engagement of the sites but also with the strategic -- the feedback of the strategic partners that I mentioned.

This just gives you a sense of what we did. We kept track during the trial, are we

meeting our goals at various sites and providing feedback throughout the course of the trial to those sites if they weren't doing it, and actually found some interesting findings in the trial, and there are differences in outcomes of women as compared to men. There are differences in outcomes in certain minority populations as compared to the Caucasian population. We did find data that suggested that this was unrelated to the devices that were studied -- I want to make sure our FDA colleagues know that -- but are important in terms of that we do need to understand and recognize the heterogeneity that we see in outcomes in these different populations as we approach -- as we try to develop approaches to improved care.

I want to close by talking about a separate initiative, which has been an initiative where we are adding patients as full voting members of the steering committees of our pivotal scale trials within my group. Why do we do that? I think we've all heard already the need to be much more patient-centric. I mean, the only value that we create is value that we bring to patients. And what we are asking and why we want to have patient representatives on our trials are to help answer three important questions.

First off: Is what we're studying in the trial meaningful to patients? Because again, if it's not, then I don't know why we would do it.

Second: Are the materials that we're developing for patients in the trials clear? Are they relevant?

And then, finally, based on the trial design and based on what we learn during trial conduct, what's the impact of participating in the trial on patients both in terms of time commitment, travel, expenses, but also just the actual interventions that we're asking patients to undergo? Is the trial unduly burdensome?

I'll tell you a little bit of some of our lessons learned in doing this. The first lesson that I want make sure you all hear, and that my colleagues all hear, is that this has been an

unequivocally positive experience for us. The only regret I have -- and I really want to make sure you recognize I'm not coming at this from any kind of feeling of being self-congratulatory. In fact, it's the opposite. I am really humbled that it took us this long to get this far, and I really wish we had started doing this a decade or more ago.

We did have to develop what are our expectations, how do we identify who's the right patient to be on the trial. We do prefer that it be a patient who has the specific condition that's being studied in the trial, ensure that their feedback is relevant. We solicited nominations from some of the investigators in the trial, the study PI or other steering committee members. Again, we've made it very clear that this is a full-fledged, full voting member of the steering committee with the same roles and responsibilities as the academic physicians who, on a steering committee, had to work very hard with our legal group to make sure that we were compliant and that we understood what we needed to do in terms of contracting, payment terms. We've got really good processes for defining fair market value for physicians and allied health professionals. We didn't have anything at all like that for patients.

I can share with you a couple success stories in 20 -- oh, I'm 20 seconds over. Maybe I'll just go through these very quickly. Again, provide very important feedback. We did have a bit of a struggle identifying patients, and I think we need to get our academic partners more used to doing this. We also needed to work on internal policies in terms of travel. And also I do want to say we had a contract with one of the patients that was specific to the trial, but then ended up asking that patient actually to represent us at an AdvaMed patient engagement event and had to then figure out how to revise the contract in order to be able to do that. But overall, I'd say it's been an extremely positive experience for us.

MR. CONWAY: Great. Thank you very much.

Our next presentation will be from the Patient-Centered Outcomes Research Institute.

DR. CARMAN: Thank you. Hi, good morning. As usual, at this time of the year my allergies are terrible, so I apologize for my voice. I have some water here to help me, depending on how that goes.

I am delighted to be here for your inaugural meeting. I am the Director of Public and Patient Engagement at PCORI. But before going to PCORI, I was actually an inaugural member of their patient engagement advisory panel, and actually Suz Schrandt, who's sitting over there, was at PCORI at the time. I hope that you find your experience, this PEAC, as rewarding and fascinating as I found mine at PCORI. It was really a rich experience. I was invited onto PCORI's PEAC when it initiated because I was a researcher and a practitioner of patient and family engagement in care and delivery, as well as thinking about it in research, so I wanted to share that as a little piece of background.

PCORI always likes photographs. Thanks. There's my photo. I realize that I must look like I do Garanimal clothes, I know. Blue and black and gray, and they go together, and that's pretty much how I handle talks. So I think I'm not going to use a photo next time; it makes it a little obvious. I also just really want to congratulate FDA on this activity and the staff. They have been wonderful and supportive and terrific to work with in doing this talk as well.

So what did they ask me to do today? Well, they asked me to give an overview of key issues in recruitment, share a bit about what we've learned about the importance of patient and stakeholder engagement, and provide an overview of what we have learned around study recruitment and enrollment and explain how this is making a difference. I am going to note that Dr. Tarver's presentation of all the work that everyone did yesterday and some of the other things have really meant -- but there are portions of my talk I'm not going

to spend much time on. You guys know this, you've learned about it, and you've got a lot of amazing ideas already. There was a pretty impressive amount of work done yesterday, so I'm not going to spend too much time on that, some sections, but I'll let you know when I'm past, too.

I always like to explain what PCORI is. I know lots of folks here know, but not everybody, necessarily, in the audience. So we're an independent research institute. We were authorized by Congress in 2010. We have a 21-member board of governors from the General Accounting Office who puts those members on our board. We fund comparative effectiveness research, right? We compare treatments of varying kinds and approaches, and that's PCORI's primary research function, is to comparative effectiveness research, and importantly, we seek answers to real-world questions, right, about what works best based for patients, based on their circumstances and their conditions. And I think that's a really important component.

Just a couple things about PCORI's strategic goals: PCORI's goals are really to increase the quantity, quality, and timeliness of useful, trustworthy research and make it available for healthcare decisions by all stakeholders and patients. PCORI also wants to speed the implementation and use of patient-centered outcomes research evidence and influence research funded by others to be more patient centered, one of the reasons that I am obviously here today and sharing a bit of PCORI's perspective.

And just as a quick reminder, our research has to meet six criteria: It's got to fill critical gaps and evidence. It's got to be able to be adopted in practice. It has to have merit, of course, right? You still have to have scientific merit. Investigators and environment matter. It also has to be patient centered, and it has to have patient and stakeholder engagement.

So I want to spend just a second after this talk, I just -- I always include this to give

people an idea of the work that PCORI is ultimately funding, which really focuses on the highest-burden conditions and treatments and care and approaches for populations. So just a bit of background information on what we're funding.

But there was some discussion previously, you know, what do we mean by patient centeredness and patient and stakeholder engagement? And as Sue well knows, PCORI has spent an awful lot of time thinking about this, and per the previous talk, PCORI focuses on projects that have to focus on the outcomes that matter to patients and in the context of their preferences. So that's really what patient centeredness means. What you're going to study has to really focus on that, and it has to reflect what's important to them.

And for engagement, it means patients and stakeholders and partners -- sorry, patients in research are not just subjects, but they're really partners. I'll talk a little bit about the continuum, but that's the point here. They're not subjects or objects of research but partners in it. And it's an active and a meaningful engagement between the patients and scientists, and involvement really exists throughout the plan.

And, you know, another thing I forgot to mention at the start of the talk is, you know, I really did think about this talk compared to some of the ones you've just had because this is a wide-angle view, right? You had some telescoping talks about particular studies. Here I'm going to give you a wide-angle view on what we've learned, rather than by specific project, but I will give you a couple of cases at the end. But the perspective I bring is a broader crosscutting one.

I do want to share this as well, because there's a lot of conversation today about involvement. I think we often talk about an insider/outsider perspective of PCORI's. I mentioned I've been at PCORI now as -- working for probably about 7 months. I think what's unique about PCORI is the soup-to-nuts approach to engagement, right? So it's all the way from getting input into what are the topics and what should be priorities, getting to

the actual question, then involvement and support for involvement in the conduct of the studies to the actual -- and that includes everything from input into the questions, recruitment, which I'll talk about specifically, we'll sort of telescope into that a little bit, but also interpretation and dissemination and in participating in that process, which I think is really crucial.

Another key piece I'll just mention, because it came up today about getting research findings back to the communities who participate. PCORI also requires public reporting, so PCORI publicly reports on its site a summary of every study as it's completed for lay and scientific audiences, and that's a real commitment to ensuring that those findings are available to the communities that have participated in studies. But I think this whole continuum of involvement is crucial to understanding some of what PCORI has learned.

So I was asked to provide a little bit of an overview of the -- you know, the challenges to recruitment, and I think you all know a lot, that it's a huge challenge, and obviously, inclusion of people in studies is enormous and challenging, and I think it's a particular challenge right now because at the same time people are already struggling to recruit for studies, there's increasing demands, obviously, for greater participation, right? So it's just a huge ongoing issue.

And this is a section, as I said, that you've talked so much about already that I'm going to spend a relatively short amount of time on. I was going to start with just a bit of background information, which was just how much Americans have heard of trials, which is what Research!America's work shows us about how few people actually participate. So while folks have heard it, they really have not been able to participate, and when you ask them why they think people aren't participating, it's the things that you would expect, right? Not aware of how to do it, they don't trust, it feels too risky, worried about adverse outcomes and those kinds of things. So there's a lot of challenges to participation.

I did want to note that one thing I like to do is kind of bucket and categorize things, and I think when you think about the challenges to achievement of goals generally, in recruitment, fall into three big buckets. It's patient and participants, it's investigator and clinical sites, and it's study protocols. So I've included a slide here on some data from systematic reviews, which are suggesting some best practices, and I leave it with you as just some fodder for some thought; I'm not going to spend much time here.

Also, some trends in the field. And you all have been talking about them today. I'm going to move, though, pretty quickly to what we know from PCORI's work, but I think it's an important context for what's happening in the field because while PCORI is a practice-based environment and we're learning from our own engagement, obviously we're also looking at the literature in other fields to understand what's going to work. So let me talk a little bit about what we know from PCORI's work.

And the other thing is, I'll just note that on this notion of continuous learning, we have a lot more information that we're collecting and accumulating that we'll have in the coming months. That may be valuable for you all to think about as well.

So I want to give you just kind of a big picture of PCORI's benchmarks at its current state. So I think we've got maybe 500 studies now, 460. Don't quote me on that ballpark. The good news for PCORI is we're doing okay in terms of this area right now. This is a very broad comparison, all caveats aside, but our non-completion rate is a bit lower, and about 70% of our projects meet their timelines, and our timelines are extended, on average, about 6 months. We do have the contractual ability to extend timelines, which is what's nice for PCORI, but we -- while we, like everyone, have our challenges, at this date and time we're at least doing okay. Lots of areas to improve, of course.

So I mentioned to you that we engage stakeholders throughout the entire research project process. This tells you what stages. So in our projects, basically in 3 out of 5, they

involve patients at all stages. About 71% of our projects involve patients and stakeholders in the recruitment or retaining study participants. So a big portion of our studies do include patients and other stakeholders in this process.

In addition, when we ask researchers what impact or influences this had, they believe that stakeholders and patients have a pretty big influence. So, ultimately, about 84% report a moderate to a great influence.

And inspection again of that involvement is sort of everything from input to partnership and collaboration, so this slide isn't going to tell you where it fits on the continuum, but to let you know there's a wide range, and I'll give you some specific details of the way that patients, in particular, have supported in recruitment. So they've provided strategies for recruitment, help in developing outreach and screening tools, been a liaison between researchers and patient groups. In some studies they've done actually on-the-ground recruiting and practices and working with partner organizations.

These are just some quotes from organizations, giving you a little bit more context for the kinds of ways in which our participants have been supportive, and these are quotes from the PIs in the studies.

So the most common activities are really here, which is guidance and feedback on the materials, approaches to recruitment, ensuring ongoing data collection. The effects from our PIs, as they describe the effects of this participation, is much more patient-centered recruitment procedures, recruitment materials and -- sorry, retention procedures. And, ultimately, in their studies they feel that's provided more robust enrollment and retention in the studies where it's had an influence.

And, remember, our challenge is back to patients and participants, investigator and clinical sites, and study protocol. I think one of the key messages I want to convey today is that patient and stakeholder collaboration can make a difference in all of those areas

because people can give insights not only to what sort of works for them, but what would be a better protocol and some methods and other things. So it's a terrific resource.

I always like to include a concrete case because we all take in information in different ways. This is just a nice slide from a terrific study by one of our collaborators focusing on a comparison of surgery versus antibiotics. Got a lot of suggestions from stakeholders about how to improve enrollment and retention, and these are just two examples, actually, about making the enrollment script more patient- and family-centered. They gave them concrete ideas, suggested an online follow-up procedure for retention, and from the PIs' perspective, they think it had a substantial influence on the enrollment from the trial going from 65% to 95% and retention going from 58% to 85%. So like some of the stories you've heard before, those are really concrete, important, and valuable outcomes and that's just really illustrative.

Given the time, I'm going not go into this, but this is just another illustrative example to make a little bit more concrete, not only in the recruitment procedures, but also in what you study and how important it is if you focus on what people care about and the outcomes they think is important to them or the treatment and delivery option. They're much more likely to participate, which you've also heard, so it's kind of a little bit of an anchor point on that as well.

I was also asked to spend just a few minutes thinking about recruitment and retention in underserved populations. Again, this is a little bit of a down payment today. We're actually doing a much deeper dive that we'll have data on in the near-term future, which I'll mention at the end. So this is just kind of take this down as sort of a down payment on this conversation.

As always, in this talk I wanted to note some external resources that you might want to think about using, and I'm not going to summarize all of this because that's not sort of

my role here today, but these are some really important systematic reviews and other resources you might want to take a peek at in your own thinking about these issues.

So what do we know from our PCORI studies? Well, our addressing disparities team. So PCORI has a tremendous focus on addressing disparities and studies focusing on this when we are looking at inclusion; obviously, it's not just in those studies, but across those studies. But that particular team did a qualitative analysis across a sample of studies in 2016, and they were trying to look at, sort of, these barriers and facilitators. And the barriers are going be ones that are going to feel consistent with what you've heard previously here today, in terms of time and transportation, concern about academic settings, right, and going into those places, as well as historical mistrust.

Facilitators: Something to think about, really, on the engagement side is really finding those cultural brokers, mediators, and key influencers who can really negotiate the community and the researchers, who can really help to bridge that. And we have found addressing head on the mistrust is the best strategy, to have an open dialogue about that and acknowledge that.

And in recruitment, if possible, have people from the community really troubleshooting challenges with the team because they really understand better than anybody what those challenges are.

I mentioned that we had some initiatives. That's the down payment on some future state information.

And I just want to conclude with three core things to remind you again. The three areas, whether it's recruitment and retention issues or problematic, is patients and participants, right? So you have to understand what's their point of view, what do they care about, what do they need to participate. And you have to focus on creating those facilitators and removing barriers, as well, as those key motivators for them to be in the

study.

The investigators on the clinical side, patients and stakeholders, can provide input into training, planning, direction and outreach. Through direct engagement with them, they're going to help you solve those problems.

And even in terms of the study protocol, while the study protocol has to address a lot of issues, we have also found that patients and stakeholders can provide some key insights to ensure that those protocols are going to be effective and get you where you want to be.

Thank you very much for your time.

MR. CONWAY: Great, thank you. And thank you for your down payment.

The next presentation that we'll hear is the National Organization for Rare Diseases.

MR. MELMEYER: Well, thank you. And good morning, everybody. I am Paul Melmeyer. I am the Director of Federal Policy at the National Organization for Rare Disorders, and I'm very pleased to be here this morning, but I'm actually even more pleased that you all are here this morning. As a patient advocate, we became aware of the potential of this Committee to be made about 2 years ago at this point, and that was a fantastic idea then, and we think it's a fantastic idea now, and we're really excited to see the contributions that you all will make to CDRH processes going forward and just to see the inaugural Committee here today.

So before I get into recruitment, enrollment, and retention within the rare disease patient community specifically, I just want to do a little bit of a review on rare diseases and who NORD is. So a rare disease is any disease that affects fewer than 200,000 individuals or fewer in the United States. That amounts to about 30 million Americans with a rare disease. There are estimated about 7,000 rare diseases within the United States.

So within the rare disease patient community, most patients go through a diagnostic

odyssey that takes 7 years, oftentimes longer, for an individual -- goodness gracious, an individual with a rare disease to finally find a diagnosis is because rare diseases are oftentimes genetic in nature, there are oftentimes very few individuals with the disease, obviously, and they are oftentimes very heterogeneous, so they manifest very differently within the patient population.

There is a general lack of knowledge within the medical community on these diseases. There are very, very few treatments. Only about 350 or so rare diseases of the 7,000 in existence have a treatment, so that means 95% of rare disease patients have no treatment that's indicated for their disease specifically, and then this would also lead to many reimbursement issues.

So about us: We are a patient organization that was founded following the passage of the Orphan Drug Act in 1983, and ever since, we've been advocating for rare disease patients. I'm going to skip through this stuff in the interest of time. I'm going to try to catch us up a little bit since we're running behind. But we have various different initiatives and programs to -- that are directed at the rare disease patient community, including our policy office here in D.C. representing rare disease patients at FDA, NIH, or up on the Hill. And then our headquarters in Danbury, we have various initiatives, including a membership program for very small rare disease patient organizations that may only have perhaps one or two or three full-time employees. We did a survey of 260 members a little while ago, and we found that 70% of them had fewer than five FTEs, so these are really tiny family foundations who are generally representing the rare disease patient population in question.

Various other programs here including a program to develop rare disease patient registries for our member organizations as well as patient assistance programs, and I'll speak a little bit more on those in a minute.

So before I get into recruitment, enrollment, and retention specifically, I just want to

talk a little bit about the unique challenges that rare diseases will bring to clinical trials. We talked a little bit about the difficulty in structuring and setting up trials already this morning. Now, multiply that several-fold for rare diseases for a variety of reasons. First of all, we're dealing with incredibly small patient populations oftentimes. Of the 7,000 rare diseases, some are closer to that 200,000 prevalence mark, but I would say the vast majority of them are actually on the other end, and they may only have a couple hundred patients in the United States with that specific rare disease, maybe even fewer than that and maybe only 20 known patients in the entire world with a specific genetic mutation. So imagine trying to structure a clinical trial with only 20 individuals with that specific genetic mutation. Now, of course, that's at one end of the spectrum, but this is something that device companies who are developing oftentimes -- use devices have to consider.

In addition to that, this creates a very dispersed patient population. Since these are genetic in nature, they're generally pretty evenly dispersed across the United States or across the world; there's really no clumping, in a sense, of individuals with rare diseases. Two-thirds of rare diseases affect children because these are genetic diseases. Oftentimes, individuals are born with these diseases and so hopefully, they're diagnosed early, but they are genetic in nature oftentimes, and it's a lifelong condition that the individual will live with. Of course, hopefully, with gene-editing technology, maybe that's not the long-term thing, but that is the current situation we currently live in.

As I've already said, the diseases oftentimes manifest quite heterogeneously and oftentimes include many comorbidities; they're multi-systemic, they're very severe oftentimes, they're very debilitating, and so this also can lead to various significant financial constraints for families that have either a child with a rare disease or perhaps an adult with a rare disease. Because the disease is so severe, it requires a lot of -- really, an immense amount of care oftentimes in the home and a specialty facility. Many specialists, many

drugs, many devices. So the cost can really add up. So just an additional consideration that should be considered when structuring trials.

All right. So I'm going to go through just a few points on our perspective on recruitment, enrollment, and retention within the rare disease patient population and really throw out -- I want to emphasize the importance of involving the patient organization that represents that specific population, really, throughout the entire process, from the very beginning, in which the device company is considering developing a device for a specific condition or a specific symptom, all the way until when that device is on the market. Now, obviously, that's not your concern, but I just really want to emphasize why and how that patient organization and the patients, themselves, should be involved throughout the entire process.

The first point I want to make on recruitment and enrollment, specifically, is the importance of patient registries, and anything from just the very simple contact information registry all the way to a comprehensive longitudinal natural history data registry, and just the importance that these registries play within several different -- several different facets of progressing towards a treatment for a rare disease, but especially within clinical trials.

And one example we've heard from one of our member organizations that has a patient registry is that they were actually able to fill a clinical trial within 3 weeks because they had a comprehensive registry of patients with that specific disease. And within the registry, they also captured where the patients are, so that can help govern where the trial sites are within the clinical trial. They had willingness to participate within a clinical trial, so they could reach out to those who would be most excited, I suppose, to participate within a clinical trial. And in talking with this specific organization, it was so clear just how proud they were of being able to contribute to development within their disease by having a registry, and being able to partner with the specific company and being able to fill a trial

within 3 weeks, that's completely unheard of, especially within rare diseases. So the importance of registries really can't be understated, essentially, within recruitment and enrollment, especially for rare disease devices.

Use of social media, I'll throw that out there: It's kind of a buzz word at this point, kind of a broken record thing. But the patients really can be best reached oftentimes not only just through Facebook and Twitter, everyone knows about that, but through Instagram and Snapchat and really innovate social media methods that perhaps patient organizations, but especially companies, haven't caught up to yet and could really reach a diverse -- more diverse population through kind of diversifying the way that they try to reach out to patients and enroll patients within their trials.

We've already talked a little bit about considering the structure of clinical trials and really involving patients throughout the development of the structure of a trial and then, as a trial moves forward, just some additional considerations that should be made as patients -- the patients can contribute to the inclusion and exclusion criteria for the trial. This is quite important because patients and patient organizations can contribute really expert knowledge on the potential criteria that a company may be placing on who can enroll and who cannot, and I'll talk a little bit more about those who cannot enroll in a minute.

But I mean consider, for example, a family with several children with a specific rare disease who are approached for a child to participate within a trial, and perhaps one child has actually progressed too far and so they're thus hitting the exclusion criteria, think about how difficult that would be for the family to make that choice for the other child to potentially participate while the other cannot. Some things that if the patient organization and patients are involved can be considered beforehand and can be -- perhaps the trial can be structured in a way so that those choices aren't as difficult for the family.

The location sites, as I already mentioned, can really be tailored to the specific

patient population if the patient organization is involved, because they know where their folks are and they know where the patients are, and they can really contribute to where best the trial sites can be located.

The duration and time of year: I'm going to -- one point on the time of year very briefly. This may not seem as a particularly salient point, but there is a patient-focused drug development meeting for narcolepsy that we attended a few years ago, and what all the companies found in the audience of that room was that you shouldn't put a narcolepsy trial in the winter because it is so much more difficult for individuals with narcolepsy to participate. That's something they hadn't considered. If the patients are involved in that initial structuring of the trial, they would know that; they'd put them in the summer, and the trial would be more successful.

And then, finally, just keeping in mind the full ecosystem of the patient circumstances, not only the patient, but the entire family and the caregivers and keeping in mind when the school year is, if a child is going to be participating, or the parents' job situation or just anything that can contribute to the ability of that family participating within the trial should be considered and should be thought of up front in collaboration with the patient organization.

This is a graph that I shamelessly stole from Beroe Analysis. This is just a quick -- kind of a graph of methods for recruiting patients and then the impact that it has on patient recruitment, and I want to emphasize that top right box or top right circle, I should say, over there. Patient support forms and registries are the most effective way of recruiting patients.

In addition, additional considerations around recruitment, enrollment, and retention. I'm going to skip to the second one, and this is around considering those individuals who are excluded from the trial. And I'm sharing that there is a systemic way for

offering assistance or at the very least, working with those patients who cannot participate in accessing the device through expanded access or in some other way assisting this patient to -- it's very difficult for some patients to be able to participate and some not, and it's incredibly important for a company and that patient population to determine how to interact with those patients who are unable to participate and offering some sort of support either through expanded access for that device or through some other means. But this is not something that should be thought of when those patients come looking for that device or drug or biologic later on and all of a sudden the company is surprised by this and has absolutely no plan on how to deal with these individuals. This is something that needs to be thought of as the inclusion and exclusion criteria are being considered.

One thing that we found was very successful in retaining patients in clinical trials is an emphasis on in-home and local clinical trial support, in-home either through telemedicine or through other reporting of symptoms or monitoring or, you know, whatever can be done in the home with a patient should be done in the home with a patient to really relieve the burden of that individual having to go to a trial site. If that can be done in the home, let's do it there.

And in addition to that, perhaps if lab work needs to be done, partnering with local labs so the patient wouldn't have go all the way to the hospital or all the way to the trial site, they can just drive down the street and have that lab work done, and then that can be contributed to the trial.

Travel and lodging assistance, we find, is incredibly important for our patient population to ensure that it's not a financial burden on them to get to a trial and to have a place to stay at the trial. But also kind of creative ways in financial -- so this is just with the hotel, not just with the plane but also with, let's say, entertainment, for example. There's one example that we're aware of, of one of our fantastic member organizations, the Parent

Project Muscular Dystrophy Foundation, that they had, in a sense, an entertainment assistance program that kept the boys who were participating within the clinical trial entertained in the evening. They would go to a baseball game, they would go -- they had things to do; they wouldn't just be sitting in the hotel waiting for the next day to participate in the trial. These aren't always things that kind of come to mind, but these are things that patient organizations can say it's absolutely critical to have entertainment for the family, have things for the family to do to keep them in this trial as they're there at the site.

Provision of psychological and emotional support: Trials can be very difficult for individuals, whether it be the side effects that can result from participating within the trial or perhaps if a trial is not being as successful for that specific individual, having those support systems there for them to tap into and to be ready to assist the patient if those situations arise.

And then finally, just return of information. There's a limit to what companies can return to patients on how well the trial is going or the contribution specifically that they've made, but patients want to know that they've made a difference and they're going to be much, much more willing to participate in the future if they know that they made a difference in that trial. Perhaps the trial was successful and it's because, you know, they were there and they were participating. Perhaps a trial was unsuccessful, but at least having gratitude from the company, just thank you for participating, thank you for being here, you made a difference. We find that to be important as well.

And I'll close there. Thank you.

MR. CONWAY: Great. Thank you very much.

Here's exactly what we're going to do. There's a break that's scheduled for 11 o'clock, but before that break -- and I know you folks are hanging with us and I appreciate it, but if you could indulge us, we're going to do 10 minutes of quick-fire

questions and answers, and for my Committee colleagues here, quick-fire is precise questions. For the respondents, it will be precise answers back. We'll keep it strictly at 10 minutes, then we'll do the 10-minute break and come back in.

So I'll defer to -- okay, Deborah. Go right ahead.

MS. CORNWALL: Deborah Cornwall.

I have a question, really, for all of the speakers so far, and that is, are there any standards that exist for defining the target population or the demographics of the population that you are seeking, to ensure that they are parallel to the patient population? I was particularly struck by the Scripps example of, you know, the young men, which excluded an enormous amount of the population. And so I'm just wondering, are there -- I know there are cancer registries. To what degree are there registries for other diseases, and to what extent are there any common standards that the FDA or anyone else uses in evaluating the results of the clinical trial?

MR. CONWAY: So for those who would like to answer, come on up to the microphone and identify yourself.

DR. STEIN: So Ken Stein.

I can go quick from a cardiovascular perspective, in particular. There a lot of registries with a very good understanding of the overall demographics of disease. We like to see that the population involved is representative of the overall population but with the caveat that there's also a needle for time to ensure that we've got adequate data even in relatively small populations to ensure safety and efficacy in those populations as well.

MR. MELMEYER: I'll just echo that point as well. We ask that trialists are as representative of the target population that could be benefiting from that device as possible, to perhaps move away a little bit from just focusing on getting that successful p-value and actually consider the full population that could be using this device and ensure

that they are represented within the trial.

MS. CORNWALL: So "as possible" is an operant.

MR. MELMEYER: Right. And that's still not particularly well defined, just representative population. It would be a lot better to have more work done on that. What does that mean exactly? But that's kind of the catchall --

MS. CORNWALL: Thank you.

MR. MELMEYER: -- that we use.

DR. CARMAN: Yes, Kristin Carman.

Obviously, I cannot speak for the FDA, but it is -- particularly in PCORI studies, they're required to think about heterogeneity, right, in order to have real-world findings. So it's a very crucial component of our studies, is really trying to focus on who this might affect and including them in the research studies, which is why there's so much focus on the recruitment and retention.

MS. CORNWALL: Thank you.

MR. CONWAY: Great, thanks.

Dr. Blackburne.

MS. FELICIONE: Elise Felicione from J&J.

So speaking along the lines of what -- the case study that we shared, we have to -- I don't know that there are a set of standards that we follow, but it's one of those things that we have to have in mind. We're designing global trials often, and that even broadens the insights that we need, you know, beyond our borders, thinking about who will be -- what is the makeup of the study population, the demographic, and making sure that when we seek patient insights, that's represented by the different -- the heterogeneity of that group.

MR. CONWAY: Thank you.

DR. BLACKBURNE: Hi. Rose Blackburne, Industry Representative.

And my question is primarily for Dr. Stein. And, Dr. Stein, I don't know -- I'm a board certified OB/GYN, but I've been in industry for a while, so my question is around your WIN-Her. I really appreciated that case study, and I'm familiar with a lot of the work, diversity work, at Boston Scientific. But did you notice a difference or did you try to look at differences in enrollment in cardiology PIs between male cardiologists and female? And then similarly, you touched on it a little bit, have you integrated or outreached specifically to OB/GYN, family practice, even at the level of ACOG or AAFP, to see the differences in how they refer? But specifically for cardiologists, do you see trends between male and females enrolling women patients?

DR. STEIN: Sure. So Ken Stein.

I'll answer with two different components. We haven't reached out specifically through ACOG directly to obstetricians/gynecologists. But we again, through WIN-Her, again realized that, again -- and particularly women, but again it's difficult to generalize. I think this is actually true of everyone that, you know, a lot of people go back to their primary caregiver, and for women, that does tend to be obstetricians/gynecologists. And so we've developed materials for our investigator-physicians to use to give back to those kind of primary care practitioners.

In terms of whether there's a difference, we've made -- we are making an effort to include more diverse representation among the PIs of our trials. We haven't looked at it within trial enrollment, but we have looked it at just within device usage. And so if you look at female electrophysiologists versus male electrophysiologists, implantation of ICDs, there's a big disparity between men and women. Women electrophysiologists do statistically better than men, but it's only a marginal, very small difference.

MR. CONWAY: Thank you very much.

DR. BLACKBURNE: Thank you.

MR. CONWAY: Coming over to Cynthia, quickly, and then we'll go to Dr. Parker.

MS. CHAUHAN: Mr. Stein, this is for you. Cynthia Chauhan.

I appreciated much of what you're doing. I particularly appreciated your comments about researchers having questions, patients having needs, and bringing those together. My concern is in choosing your advocates, at least the one you showed, you didn't move outside the medical community, and I would really appreciate it if you would consider moving outside of the medical community to non-medical people for advocacy, because it is a somewhat different voice.

DR. STEIN: Agree completely. And we have made an effort to do it. The one example was someone, you know, who is a physician but not within the specialty, but in other cases it's been non-physicians. And really, I appreciate the point you're making, and I agree with it completely.

MR. CONWAY: Dr. Parker. And this will be the last question.

DR. PARKER: Okay, this is for Dr. Stein.

And just for information, WomenHeart is an organization that does have women advocates who are heart disease patients who are actively involved in the advocacy efforts. I know that from another women's group that I'm in.

But my question to you is -- and I applaud your efforts for Boston Scientific, and I certainly hear your passion for equalizing things, but for your strategic partners, did you incentivize them in any way? What was your relationship with them in order to get them to refer patients?

DR. STEIN: So I'm not sure -- we engaged them as consultants in these efforts. We didn't engage them directly to refer patients, so that was more -- this is not speaking of Platinum Diversity. It was engaging them both in advice around trial design, but also in terms of helping us with site selection but then still rely on the sites to identify and enroll

patients.

DR. PARKER: Okay, but they weren't necessarily compensated for their input?

DR. STEIN: I don't know the answer to that.

MR. CONWAY: Great. Thank you very much.

At this point, just out of curiosity, for the first two panels this morning, the speakers that presented, how many of you folks will be here this afternoon when we get into our more extended Committee discussion? So that's great. So the Committee can take a look at that. We have extended time this afternoon, and I think we'll go ahead and pose some questions. At this point it's 11:12, so we'll be back here precisely at 11:22 to start again. Thanks.

(Off the record at 11:12 a.m.)

(On the record at 11:25 a.m.)

MR. CONWAY: Okay, folks, we're going to go ahead and start now.

The third topic of the morning is Communication of Study Results to Trial Participants. The first presentation that we'll have for this is from ClinicalTrials.gov.

DR. ZARIN: Hi. I'm Deborah Zarin, the Director of ClinicalTrials.gov, and I'm delighted to be here.

UNIDENTIFIED SPEAKER: A little louder, please.

DR. ZARIN: Okay. I'm Deborah Zarin from ClinicalTrials.gov. Can you hear? Okay. Let's see, let me just see if this works. Okay, great. I was going to talk about considerations in reporting results of clinical trials. I was talking about both reporting results to the people in the trial, as well as the general public.

So in 2007, as the result of the Food and Drug Administration Amendments Act, ClinicalTrials.gov was directed to develop a mechanism for reporting structured results of clinical trials, and in doing that and following the law and various scientific reporting

standards, we essentially defined a minimum reporting set which focuses on the objective results of the study, prevents cherry picking or creative selection of which results to report, and is based on accepted scientific standards. This minimum reporting set is now codified in the regulations that were finalized about a year ago.

It consists of tabular data instead of narrative text, which was designed to avoid and/or minimize opportunities for spin. These were all problems that were well documented in both the published literature, the published peer-reviewed literature, as well as in things like press releases and other less formal ways of reporting results.

It also avoids interpretations as opposed to facts. So if you look at the results on ClinicalTrials.gov, it's literally just what happened in the study, the quantitative depiction of what happened in the study without conclusions.

So this was designed as a resource for the scientific community and not specifically designed for the lay public. It was designed to benefit the public as a whole, but the particular resource, this part of ClinicalTrials.gov, is designed for the scientific community.

And this is, over on the left, just a set of tables. These are, of course, empty tables, but to show you what we mean, it's a bunch of data tables.

So concerns about posting narrative summaries of individual study results, we studied this. In fact, the law told HHS to determine whether or not to require the posting of lay narrative summaries, and in the regulations that were finalized a year ago, HHS declined to do that, and there were many reasons, but here are some of them.

One is that -- the way I call it is that one study is really hardly ever the meaningful unit of analysis. So each study I think of as a link in a chain, and sometimes the chain is fairly linear, and a lot of times the chain is more like a web, I guess. But not all chains are straight lines, and not all links are particularly interesting in and of themselves. And if anyone feels like it, they could look at ClinicalTrials.gov and just look at -- you can choose to

look at just the studies that were registered in the past week or the last month, and you'll see all sorts of things there, most of which wouldn't be of particular interest other than maybe to the scientific community studying that very narrow question. Okay.

Second, summaries, by their nature, end up being subjective so whose perspective is the right perspective? Certainly, from the point of view of a government website, we determine that none of these perspectives were the right perspective. But as you consider whether or not or how to present results to the trial participants and/or the general public, you have to think about that. Is it the sponsor's perspective, the investigator's?

By the way, this is why peer review was invented because the perspective of one individual party, especially an involved party, is generally, well, subjective. So other people are going to have different perspectives.

Then there's the problem of highly technical or earlier phase trials. These are things that might be early in that chain that I talked about, an early link or something that's answering a very small question that might be very important to the whole web of knowledge but is not going to be particularly interesting in and of itself. We see studies with 50 to 100 pre-specified outcome measures. Each one of those measures can be some very highly technical way of analyzing a particular scale that even those of us who were reviewing the data with highly technical backgrounds couldn't possibly put into a narrative sentence that would mean anything to anyone. Plus, these 50 pre-specified outcome measures could have results going in all different directions. There could be a four-arm study and in some of them -- well, it's hard to even know what better or worse might mean for some of these scales, but there's certainly no easy way to summarize that.

And then something that I left off of this slide but is really important is that even though studies that you might think of as towards the end of the chain, so you think if you looked at it casually, you would think it has important information for the lay public. The

question is this gets to the second point, subjective summaries, but there's this process of critical appraisal.

So somebody does a study, and then if you are the FDA or if you are someone who does systematic reviews or practice guidelines or even a journal editor, you're going to think about whether this study was designed appropriately to answer the question that the investigators are telling you it answered. So was it the right comparator? Was it the right patient population? Did they use the right outcome measures? Was the time frame appropriate to the question? All of those kinds of questions, those are the kinds of things that go on in peer review; those are the kinds of things that go on at a place -- at a regulatory agency like the FDA. And the question is, if you're going to bypass that, who does that? And there's problems with not doing that.

So just to show you things you know, which is this headline about this particular drug. So the information released to the media was that this is a great breakthrough; this was July of 2015. You know, November of 2016, bitter disappointment. The same drug, okay? The same study. So would it have been helpful to have released these particular results to the public with a very subjective assessment? So I'm not for secrets, I'm against secrets, which is why we -- why I work where I work and we try to get all the data out there. The question is how do you present the data and what do you make of the data?

This is a cumulative meta-analysis, so it's just if you look at the thing on the left, it's one particular scientific question, and each -- the vertical line in the middle determines whether it favors the treatment, so when the big red -- the big circles are to the left of the vertical line, those studies favored the treatment. When it's to the right, they didn't favor the treatment and the horizontal lines show the -- basically, the confidence interval, if you will.

So you could see, if you were to present the results of any one of those studies, it

might not really have told you the big picture. The big picture in this is that one dot at the very bottom which says -- with the circle over on the left, which says it favors the treatment. But you can see plenty of dots on the right that didn't favor the treatment and lots of studies where they crossed that middle line. The point is that it's the body of evidence that really is more informative than the evidence from any one particular study.

So this is a recent quote from Howard Bauchner, the editor of *JAMA*, about the value of peer review, and you can see that even for those studies that are being submitted to *JAMA*, okay, so you might think of those as the most likely to be the highest quality studies, they're still saying that the peer review that they do frequently needs substantial changes between the initially submitted manuscript and the published article as a direct result of careful peer review, editorial assessment, author revision, and post-acceptance editing. So these are the very highest quality studies being prepared in the very most rigorous manner, and the initial conclusions of the submitted manuscript frequently gets changed over the course of the editorial review until they're published, okay?

So this is an example of the sort of infamous Study 329, which GSK did of Paxil a long time ago, which purported to show that Paxil was better -- was a good treatment, a safe and effective treatment for children with depression, and I'm not going to go into the details, but a reanalysis many years later showed that, in fact, it wasn't particularly safe and wasn't effective and that same thing. So, again, this is, again, in the peer-reviewed literature there were problems, and imagine if this was written by just a sponsor or investigator without any peer review.

This is just a study with a lot of outcome measures to show how difficult that can be.

And so I'll just go to final comments. I think that trial participants have different needs than the general public. They were involved in the trial and know what it involved. They're presumably somewhat familiar with the protocol, and it makes total sense to tell

them the results of every single trial that they were in, in a way that makes sense. And I believe the general public benefits when there's broad access to complete authoritative information so that various "experts" or non-experts can access the data. And that's the kind of thing that we're trying to do at ClinicalTrials.gov to make sure that all the results are available in a timely manner.

Those who conduct systematic reviews and other such products outside of the regulatory setting would then have access to the complete data. So you want all those people, payers, patient groups, professional associations, to have access to that data, but it's not a casual process of putting that data into perspective and understanding what it means.

And, finally, I think lay language summaries can be valuable when there is something to summarize. I guess, again, look at all of the studies we get, over 600 studies registered in ClinicalTrials.gov each week, and my guess is very few of them probably would be of interest to anyone other than the people who are in the study and a very small community of scientists who are focused on that particular link in the chain. So be careful if you start talking about having lay summaries of every single study. I think that could be problematic. And I'll stop there.

MR. CONWAY: Great. Thank you very much.

We'll now hear a presentation from Sage Bionetworks.

MR. WILBANKS: Thank you. I'd like to thank the Committee for the chance to be here today. My name is John Wilbanks. I'm the Chief Commons Officer at Sage Bionetworks. We're a nonprofit research organization based in Seattle, and we spun out of Merck in 2009 with a mission to explore how open systems, incentives, and norms can change the way that we gather, share, and use biological data. And a lot of our work is based around exploring changes in roles, so the changes in roles between researchers as

they hopefully move from being individual academic labs to functioning as networks and communities, but also changing the roles of participants in the research process through things like crowdsourcing, but also through mobile clinical research, which is what I'll be talking about today.

So since we're talking about return of results, I wanted to get very specific and granular about a project we did and what we learned, because we were very surprised. It's not surprising that we were surprised by what we learned as we did the study. So several years ago we began working on a mobile research study on Parkinson's disease. The phone is actually a really effective way to measure neuromuscular degeneration. A lot of the kinds of tests that you would have in a lab that would require a participant to visit once a year perhaps can be accurately sensed using the sensors on a phone.

So dyskinesia, for example, you would go in and the clinician would either count the number of taps you could achieve in a 30-second time period or give you a rating on a scale of 1 to 5 qualitatively. You can capture all of that pretty easily on the touch screen and do that before and after meds every day. You can also do things like put the phone in someone's pocket and have them walk 20 steps and 20 steps back and get their gait, a sense of their balance. You can get a sense of their tremor from having them simply hold the phone and measuring the sensors. Also things like memory and walking.

And this creates the ability for a much deeper, more longitudinal study of a much larger population than you would if you needed to go directly. It also gives you an interface to give them back their results in real time in a dashboard. This is the kind of increase in data that you'd get from that raw number of taps. You can actually start to get more directly at other symptoms. You can also start to find people who were invisible under the previous way of looking.

So, on the left you have a 62-year-old man for whom the number of taps was a very

distinguishing benefit from his meds. So in the morning his taps would be low, and in the evening his taps would be high, showing a benefit of the medicine. But on the right we see a woman who would've been invisible under the raw number of taps count because she wasn't getting a dyskinesia benefit; she was getting a tremor benefit. So this is the value, scientifically, of this kind of a study.

And this is the kind of data that we can return to the participant. So this is one person, from the left to the right, over the course of a series of days. The red lines are days where she got a benefit from the medicine, so the bottom of the line is the number of taps in the morning, and the top of the line is the number of taps in the afternoon. Blue lines are days where the taps actually got worse after the medication. So what you can see is a little bit of the live experience where, for the first couple of weeks, there's a relatively stable benefit from the medication, and then we see a period where the benefit is all over the place. There are days when it's a negative outcome of the medication, and there are days where it's a significant benefit, and then it stabilizes again towards the right.

And so this is where we thought results return ought to look, right? This is the kind of dashboard data that you would provide back to the participants. And we enrolled 20,000 people in this study in about 6 months using iPhones.

What we found was that this was actually not a particularly good way to return results to all participants, right? We were thinking very technocratically that if we give people dashboards that show them their daily trends, that is results return and that is engagement. That may be true for a certain subset of the population, but what we've learned is something that we felt kind of -- you know, we felt kind of dumb when we wrote it down, that people are different, context matters, and things change.

And so a unitary approach to results return is not a particularly scalable or good approach to this. We have to think about people as having different phenotypes in terms of

how they want their results returned to them. Some of them don't want those results returned at all. Some of them want those results returned in radically different ways, and I'll try to unpack it a little bit.

One of the things we did was let people share their personal thoughts on what they thought was making them feel better and feel worse, and these got repurposed by our participants to tell us what we were doing wrong, both in study design and results return. It was really interesting. We had about 22,000 comments in the first 6 months alone. We had to, you know, learn how to use text-mining software to deal with it, we got so many comments. And we also saw a pretty significant drop-off in our participation on -- after the first couple of days. So what we learned is that the results return is actually really important to keeping people being willing to do all of these tapping exercises and tremor exercises. They're used to having their phones be this beautifully designed experience, and clinical studies are not used to worrying about design and interface and meeting people where they live. We've never had to do that; it's not part of the workflow or the process or the funding. If you tell a scientist that he or she needs to take money away from the clinical study and use it on design, like it's a very difficult -- are you laughing or coughing?

(Laughter.)

MR. WILBANKS: Laughing is appropriate. It's very difficult, and when we talk about results return, if we don't talk about design, this is the engagement graph that we get.

So these are some of the examples of results return comments that we got submitted through our interface. So, again, we thought, we're giving you the dashboard, you log in, and you can see all of your trends for all of your activities; what else do you possibly need? This is one of the most common typologies of email that came out, which is, you know, please just tell us how things are going as a study because we were thinking primarily that they wanted to see their progress on a day-to-day basis.

We didn't spend a lot of time communicating or designing the idea that clinical studies operate on agricultural time scales, 18 to 24 months to gather data, analyze data, vet the results, publish them in a peer-review journal. People who are interacting with their telephones don't think on 18- to 24-month time scales. They think in hourly time scales. You know, at most, perhaps weekly. And so the very idea that we would be contacting them and saying, you know, we don't have any results yet scientifically, but we've enrolled this many people and they've donated this much data, is something that a significant niche of our population wanted back as a results return.

This is another piece of feedback. This concept of summary trend reports in plain language was one of the most common requests that we got. And, again, this is not part of the normal workflow, design, funding, execution of clinical study, and so we had to stop a hierographic designer and create infographics that -- so it wouldn't be on the individual dashboards of your progress on a day-to-day basis that we could provide back. And since we didn't have at this point actual insights into Parkinson's disease, we could give people back data like this, and the response we got to the infographics was remarkable. Our engagement went back up, people's usage and willingness to perform activities went way back up. There's an actual scientific reason to do this, which is that you'll get people more engaged in the actual study.

And this concept that we have heard your feedback was really, really important. So it's not going to be this thing with the results return where we simply say, here's your data back, and we're done. Results return works best when it's a conversation where there's feedback going both ways on an ongoing basis, and it's an expectation from the very beginning of the study. It was difficult to graph this on at the end. It's been much easier, as we've started incorporating this as an expectation in every study that we run going forward, that there will be this feedback back and forth between the participants and us, not just on

the study design, because we did get a lot of comments on the study design. They would say things like do you know that when I wear tight pants, my gait data is different than when I wear loose pants? Or when I put the phone in my purse, my gait data is different than when I carry the phone in my hand? So we got a lot of feedback on all of these pieces, and treating these as a conversation, a relationship, is actually the biggest thing that we took out of it.

The other thing that we heard loud and clear was we just want you to give us a presentation. So we set up where we had a webinar, and we had a thousand simultaneous participants and this has been viewed, you know, on YouTube, not -- you know, this is not a viral video; it's not ever going to be something that gets a million views. But the people in the study, they were able to ask us questions in real time. They were able to go back and watch the video, they were able to share it with family members to explain why they were doing the strange activities with their phone, because that's another thing that we found out, is that people felt worried that they were being stared at when they were doing some of their study activities on the phone.

And so the whole kind of context of this is it's really easy to think that results return is simple, that you just mail people something back, you email it back or you give them back their individual data and you're done, or it's a paper. That will work for certain niches of the population that are enrolled, but it's not going to scale across because, again, people are different, and context matters enormously.

The other thing that we do in terms of our results return is we do give people back their raw individual data. So if you look at -- there's a little bit of a sense of who should you share your personal health data with, and should we treat study data as personal health data? Should we treat study data as a form of results and return those?

So we looked at the data back from the Health Data Exploration project. People who

were willing to -- people share their PHD with health professionals, right? They don't share it with research, for the most part, mainly because they don't have access to it. Would you be willing to share with researchers? A lot of people are willing to share their data with researchers. So we do start from the assumption that part of results return is raw data returned in a downloadable format so that people can either take that to their family members, their health professionals, or invest it into a different research study.

And this idea that this other piece of data, which is that your -- if you're going to return personal data as part of results return, you have to be very careful of anonymity and protection of it.

So this how we manage that as a form of results return. So individuals in our studies can download their raw data as a file, if they want. In this case it's not particularly useful, your accelerometer data is not that useful to third parties. But in a study, if you were to use electronic health records data, for example, this is actually a really important potential benefit. By getting my health data into the study, if I can actually download it, then for the first time I've got a copy of my health data that I can use in other contexts. So this is a piece of results return, not the scientific results, but the results of my participation in the study specifically.

And then we let people donate that data to science, if they so choose, under this concept of future independent research because most times people don't actually want to look at their data. I have my genome. I don't know what to do with it. I have a philosophy degree. But I would love to be able to get that data to people who would know what to do with it.

So this is the kind of way that we let people donate their data to science; they can give it to qualified researchers. It will be anonymized and de-identified and made available. The data users have to go through a process in which they start to have a better social

contract with the data than simply grabbing it and going; they've got to give us their identity, they have to take a test, they have to file a data-use statement, and we pass these statements' identities back to the participants so that they know that one of the results that is happening with their data is lots and lots of uses beyond the study original.

The data users also have to sign this pledge. In my dream, it would actually be a video oath because I would like the participants to be able to play a video. If Paul wants to see my data, I would like to be able to see Paul taking an oath of ethical data practice for it. And this comes from the feedback, because we're happy to have people like Paul use the data, but we want to have a sense that part of our donation to him is an ethical usage of the data. To us, this is in the same class as raw results return, raw data return or scientific outcomes return, which is the capacity to actually have an interactive relationship with the people that are using the data.

And this is the kind of data that we released. We had about 70% of the people in the study elect to donate their data to science. This is a stable number across about 18 studies that we've operated in the last couple of years. And they're able to donate survey data, demographic data, memory data. And this is what each participant would see if he or she downloaded their raw data; they would get their specific individual file of all of these responses.

But collectively, we have, at this point -- actually, this is an old slide. We have over a hundred independent researchers using this data on every continent except Antarctica, ranging from teenagers to pharmaceutical companies and tech companies. And in each of these cases, this is part of the results return. As a participant, you can see what's happening with your data and where it is, and you can even go in and say I no longer want to make my data broadly available.

And I'll stop with just the idea that when we think about results return, it's very easy

to think of it in a simplistic or narrow manner. We think it's the paper, and we get the paper back. We think it's the person's data, and we give them their data back. Or it's their trends. Oh, it's their demographics. And it's all of these things for different people at different times.

The people who want their raw data tend to be people who have a sense of urgency, someone who has an acute illness or no sense of hope from the research complex. But almost everyone wants to know progress; they want to know that what they've participated in is having some form of impact or some form of purpose. And so thinking about multiple different ways that you can provide those results is really important and then recognizing, from the very beginning, that the entire infrastructure is set up against contextual, differential treatment of people as individuals in the sense of results return. Almost nobody has the money budgeted to pay visual designers and interaction designers to meet people where they live and give them back information and results that are actually of value to them in their day-to-day lives. And intervening in that is going to be one of the most important elements of making results return have the goal of the achievements that I think we all want it to have.

Thank you.

MR. CONWAY: Great. Thank you very much.

I'd like to thank ClinicalTrials.gov and Sage Bionetworks for their presentations.

Right now it's 11:52, and what we're going to do is we're going to eat up some of the lunchtime, and we're going to do a hard break at 12:15 p.m. for lunch. We'll be back here at 1:05. We have a large number of people who have signed up to give public comment, and after the public comment period, then the Committee will be having a discussion for at least 90 minutes. It's on the schedule for 2 hours. I would expect that conversation and dialogue will be rather robust, and I appreciate speakers who will stay for this afternoon

because I think some of you may be called back for a couple extra questions.

But right now, let me go ahead and turn to the Committee. So we have about 20 minutes to go through questions and answers for the last panel.

And I'll go ahead and start with you, Deborah.

MS. CORNWALL: Deborah Cornwall.

I just have one question for Sage, and that is, based on my experience in the cancer space, the concept of sharing research is starting to gain traction, and it's gaining traction from the perspective of accelerating development. My question is, is it too early to know whether this kind of data sharing with the list of, you know, the PD research community, whether or at what point that is likely to result in accelerated treatment options?

MR. WILBANKS: I think it's hard to make substantive claims about the scientific benefits of sharing because science is exotic, right? It's science. So what I tend to -- what I believe is an ethical argument and a supportable argument is that it increases the odds, right? You're basically increasing the capacity of the system to result in outcomes. And that can happen in specific ways that can be, you know, instead of having everyone looking under one lamppost, we have six lampposts and we create a light field.

It can be we're going to be a collective map of something so that we don't keep making the same mistakes over and over again. It can be reducing redundancy; it can be increasing the likelihood of innovation through unexpected collaborations. Those are predictable and measurable benefits from sharing. But it's hard to make a leap from that to it will result in a breakthrough faster in some time period. So I tend to push against people trying to make that statement and keep them more on the "let's increase the carrying capacity of the system."

MS. CORNWALL: That's fair. Thank you.

MR. CONWAY: Dr. Seelman.

DR. SEELMAN: This is for both presenters. As somebody -- Kate Seelman is my name -- who has been very involved with disability aspects and rehabilitation, I wondered, in terms of communicating study results, to what extent there have been measures to get the information out to people with disabilities, those who are deaf, those who are blind, people who can't get to a certain place, arrive at a certain place, and how have you handled that problem or that challenge?

MR. CONWAY: I'll tell you what; if you want, why don't you go ahead and have a seat right here at the table? That way we'll cut down on the calisthenics from earlier. Apologies to the previous panel.

DR. ZARIN: ClinicalTrials.gov, which again has results but not meant for the lay public, makes everything 508 compliant. So to the extent that it can accommodate people with visual disabilities, it wouldn't really be an issue for someone with a hearing or other disability. But there's nothing really beyond that that I can say, so I don't know.

MR. WILBANKS: We've done a bad job at that. I would say we're like a lot of organizations; when you think about the funding that's required to return the results, we had to find a way to do that that wasn't funded originally. What we have done now is, we've hired -- we've hired a graphic designer and an interaction designer full time at our organization. We have a contract relationship with other designers, and part of their mandate is to contemplate visual, hearing, cognitive, as well as literacy status in all of our work, so that's ranging from -- all the way from the informed consent process all the way to the results return process. But we're still figuring out practices that actually work; we're trying to be as empirical as we can. We are committed, as a nonprofit, to open sourcing and sharing everything that we learn. So hopefully, in particular, through some of our relationships with the All of Us Research program at the NIH to be able to get some interesting and validated results to return on that in the coming months.

MR. CONWAY: Great, thank you.

Suzie.

MS. SCHRANDT: Thank you to both of you. I think my question is for Deborah.

I'm having a hard time putting it in the form of a question. I was really struck by something you said, John, that I agree with, that results return is a conversation; it's very contextual. It depends on what I, as the patient, am looking -- what's the answer I'm trying to find, the problem I'm trying to solve.

So maybe my question for you, Deborah, is when you showed us the graphic of all of these studies and sort of how to interpret them as a whole, are they all exactly the same, or might I, as a patient, want to only find the four or five that are closest to my demographic or closest to the answer I'm looking for, so that I would want to pool from a smaller body of evidence? And do you think maybe ClinicalTrials.gov could be a place where we can curate, you know, in more personalized contextual sense? If that question makes sense.

DR. ZARIN: So sure, I think I know what you're asking. When you do a meta-analysis, which is what that was a diagram of, you -- to do it properly, you would pick studies that are all addressing a very specific question and the same question, so you would want the population and the experimental arm, if you will, and the comparator arm and the measures to all be concordant or else it wouldn't make sense, right? Now, whether as a patient you might want to know, or let's say I might want to know about only studies that involve short women who are my age, you know, who have this history, then you get into other issues of scientific validity, okay?

So unlike John's presentation, I wasn't talking, and I don't deal with how to get you your -- you know, how to reflect back to you your experience in this study. That's a totally legitimate important issue, but very different from saying what does this study, as a scientific experiment, what conclusions can you draw from the results of this study when

you analyze it as a scientific experiment? And so that gets into also methodologic issues that you have to consider.

But yes, ClinicalTrials.gov can help people do that partly because compared to, say, the published literature, which is the other source, assuming you don't work at the FDA, there are, sort of, two sources of systematically available results. One is the published literature and one is ClinicalTrials.gov. And I believe they complement each other, but ClinicalTrials.gov has structured data so it's easier to say, I want to find a study of statins that use this outcome measure at the 3-month time frame. It's an easier search because the data are already put into a database in that way. In the published literature, you're doing more of a free text search. So there's those kinds of issues, but --

MR. CONWAY: Great, thank you.

I'm going to go to Amye, Cynthia, and then over to Bennet.

MS. LEONG: Thank you very much.

And thank you both for your presentations. I want to go back to a notion that, Dr. Zarin, you had said about lay summaries and I'm going to preclude -- or preface it by saying that I participate at the international level with the Outcomes Measures in Rheumatology Clinical Trials -- OMERACT -- which, based on patient participation, recommended to that particular group that lay summaries be developed for the patients and patient advocates who are involved in international research. That has since been institutionalized so that all researchers involved in OMERACT now can better understand the lay summaries, as well as the ones more directed toward health professionals.

I believe you had said, and please forgive me if I did not quote you correctly, that you did not really find a place for lay summaries on ClinicalTrials.gov. But what I also heard was there could be an appropriate place for that. Could I ask you to expound on that a little bit?

And then, John, for you to also refer to the topic of lay summaries. Have you used those in your work through mPower and other areas, and what has been the result?

DR. ZARIN: So OMERACT is an amazing organization that has, you know, engaged patients and researchers in this very arduous and detailed process of developing outcome measures that everyone thinks are important and that are measurable. And so there's this whole foundation upon which I can understand how they could present lay summaries because they've already had a process whereby, at a minimum, everyone understands the outcome measures so you're not using some scale or some measure that's hard to put into lay language because it's just very complex.

Look, I think that lay summaries are great as long as you, the non-expert, trust whoever made the summary, and I have trouble understanding how that could happen systematically in the current research environment where we know human nature. I'm not ascribing any evil intent to anyone, but I'm talking about human nature, that if I did a study I would probably spin it just cognitively in a different way than a peer reviewer would spin the same study and sometimes that spin is what matters. It's the way that it's conveyed.

So I think there are issues in lay summaries, and I think that many studies are, like I said, too early in the process to be of interest on their own. So I'd rather have a lay summary, let's say, annually or every 6 months, or it depends on how quickly a field is moving, of what's the status of research in this field today. That sounds terrific. But a summary of every single study that was done, given the disparate and heterogeneous, in terms of quality, studies that we see being done in the world, I have trouble with understanding the value of that. That's all.

MS. LEONG: And I'll respond to that as soon as we hear from John. Thank you. Well, let me just -- not rebut but add an additional comment to that, that because patients are engaged in the OMERACT model from the very beginning, from ideation all the way

through the process, that the PI is responsible for ensuring that summaries are done based on the results, based on the process, based on the methodology, and that lay summaries are written mostly initiated by the patient participants on the steering committees themselves, edited, of course, with the assistance of health professionals. So it's a team event, if you will. And so in that regard, you're right; I understand, whose perspective? I think both of you, sort of, in some ways addressed that, whose perspective are we talking about? But when you engage the patient in a patient engagement process in clinical trials, that it also includes the development of any kind of summary.

DR. ZARIN: Look, if every research project could be done in an OMERACT-equivalent setting, I'd be thrilled. So I do think that's a great model and --

MS. LEONG: Yeah, thank you.

DR. ZARIN: -- one that I think is terrific.

MR. WILBANKS: I want to follow up on your comment that it's in many ways the ecosystem and the architecture and the structures of clinical studies sort of cut against the lay summary. We're a nonprofit; we're funded primarily by federal grants and foundations. We are allowed to go fail and fumble in ways that are very difficult for the government or for corporations because we sort of view part of our job as to go fail in places and learn things.

And so I don't want to imply that I'm saying that we have succeeded or productized or solved these problems, but one of the takeaways we had from the mPower study, which is our first study, is that all of our purchase for the facing materials needed to be no higher than sixth grade reading level, from the marketing materials to the informed consent documents and processes to communications to the return of results. And since we've now embedded that in what we do, the lay summaries are generated of the study in the consent drafting process. And so creating a lay summary that describes what the study is about is

already done the day that you start enrolling. You use that to extract and repurpose the text as a study document.

When it comes to the results return, it's a similar thing, it's -- and this gets into sort of code switching and context, which is that you want to be able to provide certain documents and certain codes to the researchers because then they'll trust them enough to look at them and use them. But you have to have a process in place from the beginning, and an architecture and a structure that translates those from a single source two ways at the same time, instead of having a process that only routes them towards the researcher. It's very easy to do if your structures are set up from the beginning to do that. It's very hard to do if you haven't.

And, again, we don't have answers, we're just trying to fumble around in the space and tell people what we found out. And so we have discovered that these infographics are very good lay summary tools because they force a visual communication form as well as a text communication form. From a disability perspective, we always have a text version and a visual version so you can play one if you can't see the video graphic, the infographic. But it's mainly about trying to set up an end-to-end structure that's participant-facing as opposed to sort of grafting on participant pieces here and there. It's very hard to do the latter.

MS. LEONG: I appreciate your candor. Thank you.

MR. CONWAY: Great.

Cynthia.

MS. CHAUHAN: Cynthia Chauhan.

My initial question was answered in that. I do want to encourage lay summaries in the interest of transparency. I think your points were well taken about when to do that and it seems to me the appropriate time is after the peer-reviewed article is published. I still

think there's an issue around there's some bad studies and there are some studies that misrepresent their data. So I understand and appreciate your hesitancy, but I still think we have to work on getting -- somehow getting to that in the interest of transparency and openness.

MR. CONWAY: Thanks, Cynthia.

Bennet.

MR. DUNLAP: Hi, Bennet Dunlap.

I'm trying to figure out how to put this in a question that doesn't sound aggressive and I apologize if it comes off as aggressive. So we're here to talk about encouraging participation and retention in studies that will help devices come to market to help patients, and yesterday there was a lot of conversation about well, people should be encouraged to go to Trials.gov to find a study they can participate in. And I'm having a tremendous disconnect between the idea that if I go there as a patient and I kick around and I read some studies, I'm going to see a bunch of tables that are designed specifically to not be useful to me as a patient. Outcomes of studies, why I would want to participate in a study. And I apologize if that was aggressive, but how can we make this a process that does what we're here to do: encourage participation and retention in studies to help devices come to market?

DR. ZARIN: So I'm really glad you asked that. I understand the aggressiveness, and I need to clarify. ClinicalTrials.gov you can think of as having two parts. One is the registration part, which is where people list their studies with protocol details and eligibility criteria prior to initiation of a study, and that's the part that's there while the study is in recruiting mode and while they're looking for participants. That's the part that's absolutely designed to meet the needs of the lay public as well as the scientific community. So if you want to look for a study in which you might want to enroll, that's designed for the lay

public.

What I was talking about was the study results that yield a little more after the study is completed, which is what happened to that study, and that part is designed to be a resource to improve the published literature, to improve the information available to all sorts of decision makers, and ultimately, I think it could improve any lay summaries that were written, but it's the part when you're looking to be enrolled in a study, that part is designed for the lay public.

MR. DUNLAP: Right. And I just want to advocate for the idea that, ultimately, I am the decision maker for the health process that's going to be either my device or my children's device, and I need to be able to understand why it was approved. So I'm --

DR. ZARIN: Well, right. But you probably don't want the federal government to decide whether this set of data means that this drug is better than this other drug. So that's the thing; we're the federal government, and we're basing it on data, and we're trying to provide the infrastructure, provide authoritative information as objective as possible so that the world of the scientific community and the rest of the decision makers have access to it, but you probably don't want the government to be the one to say what this controversial study means exactly, that's all. That's the issue there.

MR. WILBANKS: And I would raise that there are some things that are hard because they're hard, and I think the translation of complex scientific tables to a lay audience is a hard problem that's hard, not artificially hard.

One of the things that we do at Sage is try to explore how abstraction and interface can create a new agency for people who are left out of the scientific process, and we've learned that there's a lot to be done there. So there could be power in requiring, you know, designers be applied to the tables, right; there's plenty of money in a device study that could be used on making sure that the results are readable. But there's also danger in it

when you abstract away from the base. If the abstraction reveals what's underneath, truthfully, it's very powerful. If the abstraction obscures what's underneath, it makes things even worse when people discover that the abstraction lied to them.

And so something as simple as -- in our consent processes we use iconographic representations of concepts and very simple summaries because that's what people click on, on phones, right? It's the picture, the headline, "You won't believe what happened next."

And so for something like the core risk in the study is to your privacy, we've had one group that said that that should be a lock, the icon should be a vault or a lock that indicates security and safety. But that's actually what we're trying to think of is risk, which is the core risk in a study is that someone might breach the vault. And so we had a different group arguing for a bright red hand, and so even with the hand, because we were trying to communicate risk. But it's very, very complicated to have a conversation of who has the authority to create that abstraction and representation and how does it get vetted when the system doesn't vet those kinds of abstractions.

I think that there's an enormous amount of work to be done there, but I would be -- let's think about a process by which you would say who gets to make the abstraction and who vets the abstraction into the lay product, because if it's done the right way, it could be unbelievably empowering. If it's done the wrong way, it could be very dystopian. And I don't have an answer, right, because these are just processes and methods that work. But there are also processes and methods that regularly get hijacked in a consumer context to keep us from understanding things.

MR. CONWAY: We have 1 minute before we break for lunch. A quick question for you, John, is this: You had mentioned text mining, and was that in the context of email or social media, in terms of the comments coming back to you?

MR. WILBANKS: So we specifically requested participants to tell us what made them feel worse or better so that we could correlate that to changes in their quantitative data. So we found things like, you know, when people aren't sleeping, their sensory data drops off a cliff because the less sleep they get, the more stressed they are, the worse their Parkinson's gets. So we did not take anything in from email or social because we wanted to be constrained to very voluntary opt-in participation than sending us free text.

MR. CONWAY: A follow-up question. Any other insights that you were able to glean about motivations for participating or did you mine for that?

MR. WILBANKS: We mined in an undirected manner. We let the software find patterns, and then we looked at the patterns. And so I would say that what we find is people participate for very different reasons, and people stop participating for very different reasons. Some people wanted to be able to track -- some people matched our expectation, and they want to be able to track their day-to-day progress over time. Some people quit because they could track their day-to-day progress over time because it only ever gets worse, right, in a degenerative illness. It doesn't ever get better. We had people straight up say we're leaving the study because it makes me feel bad to think about my condition. Didn't expect that. Now we know to plan for that.

And so what we found is that people are different, and there are typologies for any given study that emerge and in the design, in the language of, sort of, design, we call those personas or archetypes. But you don't really know, a priori, what personas or archetypes you're going to get in any given population unless you do ethnography first, but that's not generally where you start clinical studies, with ethnography. But it's actually a really good way to do clinical studies because that's how you'll get higher engagement and retention. People will tell you what they want to know.

MR. CONWAY: Yeah. Thank you very much.

Right now we're going to go ahead and break for lunch. We'll be back here at 1:05 for public comments. Thank you.

(Whereupon, at 12:16 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:05 p.m.)

MR. CONWAY: Okay, it's 1:05 p.m., and I'd like to go ahead and resume this Committee meeting. We will proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Committee, to present data, information, or views relevant to the meeting agenda.

Ms. Williams will read the Open Public Hearing Disclosure Process Statement.

MS. WILLIAMS: Thank you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

FDA has received 13 requests to speak prior to the final date published in the *Federal Register*. The speakers will be given 5 minutes to speak. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

Mr. Conway.

MR. CONWAY: Great, thank you. We have a fair number of public speakers today; therefore, I'll go over the process to ensure a smooth transition from one speaker to the next.

You will have precisely 5 minutes for your remarks. When you begin to speak, the green light will appear. A yellow light will appear when you have 1 minute remaining. At the end of 5 minutes, a red light will appear, and your microphone will be switched off. Please, if the speaker is reading for someone else, he or she should state that clearly at the beginning.

We will begin with a video presentation from Ms. Rachel Brummert, the founder of the RSB Patient Safety Coalition. Ms. Brummert is unable to attend the meeting in person.

(Video starts.)

MS. BRUMMERT: "Good afternoon. My name is Rachel Brummert, and I'm a medically harmed patient. I want to disclose that I have served as the consumer representative on the FDA Medical Devices Advisory Panel and a CDRH Panel.

"Harmed patients are the end result of what went wrong, so we are in the unique position to advise the FDA on what can be done to better engage patients. The point to patient engagement is to keep patients longer and to include them in the decision-making process. Patients need to know that their adverse event reporting won't end up in a black hole. The Access Global D System (ph.) could include a mechanism to help inform patients and their care providers. If a device is implanted, the patient and provider should be able to see if there are types of metals contained in the device and its components. If it contains nickel or cobalt-chromium, that should be on the label, similar to latex warnings.

"In addition, instructions for use should require that patients be tested for these metals prior to implant. In the case of Essure, they needed to be informed of the nickel content prior to implantation so that they could have the necessary discussion and testing

through their provider. There needs to be complete transparency to patients about risks. This goes a long way in keeping the trust of patients and also helps patients to feel that the FDA understands its duty to protect them. Any other role -- relationship between patients and the regulatory agency charged with protecting them.

"While electronic health records seek to increase transparency, patients often change providers and insurance companies, and this makes postmarket surveillance difficult to track. Patients and physicians have to wait to key information about devices prior to being on the market. The current system of pushing out a device and doing surveillance on it after adverse events are reported is a flawed system and one that needs to be fixed. We need to make this process safer for patients and less risky for physicians who want to do right by their patients and use safe and effective devices.

"In the case of devices cleared based on a predicate device, that predicate device should be reevaluated prior to clearing a new device based on that predicate. Substantial equivalence to a device that has caused hundreds or even thousands of deaths and injuries is not acceptable or safe.

"The 510(k) process needs to take more and more evidence and adverse event reports into account. For a device to be approved, it must be deemed reasonably safe and effective, but 95% are not studied in clinical trials. This presents a dire situation for patients because if a device is implanted and then causes debilitating adverse events, the patient cannot simply stop using it as you would with medication. The patient must go through -- surgery to remove -- device.

"While the National Medical Device Registry has good intentions with the creation of more comprehensive registries, there are major flaws:

"1. Registry data is only available to researchers and the data is not free; it is not free to patients or even to providers who use the device.

"2. Registries are limited to a set of devices and track the known problems. If a head implant is potentially causing neurological issues, the patient's neurologist would not need to submit that to -- orthopedic registries. That outcome is not counted.

"3. When physicians report to a registry, they often think that this satisfies the requirement to report to the FDA. It absolutely cannot take the place of the adverse event reports because the registry is not publicly available.

"The FDA allows similar reporting of adverse events, and these summaries are not readily available. The true number of reports in PubMed and MAUDE is often adapted as a trade secret or protected health information. This protects only the device manufacturer, not the patient and not the treating physicians. My suggestion to you is to incorporate patient-centered -- and to include real-world experience informed patients to achieve transparency, complete disclosure, trust, and patient relations.

"Thank you for the opportunity for me to speak today."

(Video ends.)

MR. CONWAY: We appreciate her testimony. Speakers Number 2 and 3 will be Ms. Kim Hudak. Ms. Hudak will also speak on behalf of Ms. Sarah Carlin and her organization, ASHES. Ms. Carlin is unable to be here at this meeting.

MS. HUDAK: Hello, my name is Kim Hudak, and I have no financial conflicts of interest to disclose.

In 2000 I volunteered to be a part of the clinical trials for the STOP device. STOP is currently on the market as Essure and is a permanent sterilization device. I signed up excited to be part of something that could provide a better, safer, permanent sterilization option for women. Actually, to say excited is an understatement, I was elated. I thought this was amazing.

I was told the device was already thoroughly tested and proven 99.9% effective. I

never questioned safety. I assumed that if the efficacy had been proven, safety was a given. The only possible issue discussed was a slight chance the coils would not be able to be placed, but I was assured that this was a very unlikely outcome. I was promised no down time. I've had 17 years of intermittent down time, three surgeries, and countless chronic health issues.

My excitement for being part of something new, something revolutionary, quickly dissipated as I became ill shortly after placement. My issues were disregarded, my pleas for help ignored, my complications dismissed and written off as not related to the device. My story mirrors other clinical trial participant stories. I am not unique and I am not alone. This is no longer my battle, but the battle of tens and thousands of women that have been harmed by Essure. I'd like to take this opportunity to discuss where the system failed and perhaps some viable solutions for these failures.

First and foremost, I was not informed of known potential risks. Essure contains nickel, a very common allergen. Not only was I told the devices were made of surgical steel, I was not tested for nickel allergy. The nickel allergy is a current warning of the device and at one time was a contraindication. Also not explained were the other materials such as PET fibers, which are designed to cause an inflammatory response. The only requirements for this study were acceptable health and a desire to be sterilized. I fully understood that I was volunteering for a clinical trial and that there was a possibility for unknown issues. However, the manner in which the trial was presented led me to believe the risk was nearly nonexistent. I simply was not given enough information. Furthermore, I was reassured that should an unexpected issue arise, it would be addressed and corrected immediately.

Greater focus on patient screening and full disclosure of risks is essential for the prospective participant to make a well-informed decision. In retrospect, I feel as if I fell victim to the smiles and promises of a snake oil salesman.

Essure contains two metal coils that are inserted vaginally into the fallopian tubes. A current protocol for the placement of the Essure device is, should the fallopian tube begin to spasm, the procedure is immediately stopped. During my procedure, the second device was not properly placed, it deployed incorrectly, so it was pulled out of the fallopian tube and they tried again. The fallopian tube continued to spasm this entire time. I was awake and alert for this procedure. I was afraid, in pain, and I felt like a science experiment gone wrong.

Within 3 months of the procedure, I began to exhibit symptoms such as extreme fatigue, a sharp, near constant stabbing pain in my left rear hip area, migraines, and severe PMS symptoms. All of these issues were presented at my 3-month follow-up. Yet, in the official trial records, it repeatedly says the patient did not report any unusual pain. In the same report, a note to the side said that I was experiencing pelvic cramping and pain, but it was added under "Other Health Changes." These adverse events were downplayed and some weren't documented at all.

During the first year after placement I was diagnosed with chronic fatigue, fibromyalgia, and restless leg syndrome. I was still experiencing the same sharp pain in my rear hip area. At my 1-year follow-up, I was told this was all unrelated to the device. At one follow-up I presented with a painful, blistery rash on my abdomen, as well as random rashes elsewhere on my body. I was instructed to see a dermatologist. The dermatologist had no answer for these rashes. Upon reviewing my medical records I found vague mention of this in the physician's notes, but no mention at all in the manufacturer's standardized forms. I have now seen this rash present in many other women with Essure.

On at least one occasion I was instructed to see my primary gynecologist. The doctor that conducted the clinical trials was a gynecologist. It seems reasonable to me to assume that if I was having any gynecological issues, it's likely that it was related to the

device. My concerns should have been addressed at these follow-ups, not with a doctor that had absolutely no knowledge of this device. Even more importantly, these issues should have been thoroughly documented and they weren't.

Probably the most interesting diagnosis I received was at Year 3: post-traumatic stress disorder.

As time went on, my symptoms worsened and were more diverse and abundant. I was having increasing issues with my cycles, joint and muscle pain, vertigo, and debilitating migraines, two of which I was hospitalized for. I would discuss the issues I was having and come to find out that most of these symptoms weren't documented at all. Instead of logging the changes to my health in a thorough and accurate manner, I was given a vague questionnaire filled with leading questions and little room for specifics.

In 2002 I had no idea this device was approved. At that point I was frustrated and dreaded my follow-ups, although I showed up or answered the phone for each and every one of them. I wasn't given any possible solutions to my concerns other than to seek help from different medical professionals. I was beginning to fear seeing anything at these appointments, as my complaints continued to fall on deaf ears, and I was catapulted into depression and self-doubt. I began to believe my health concerns were unique and unrelated to the device.

Most of the follow-ups after the second year were over the phone and not in person. The doctor couldn't see the color washed out of my face, the dark circles under my eyes or my painful gait. By the third year of being dismissed, I began to simply answer the questions that were presented and stopped offering detailed information. I was finally convinced by the trial doctor that my failing health had nothing to do with the device and the timing was pure coincidence.

Prior to the conclusion of the 5 years I originally agreed to, I was sent a letter asking

if I'd be willing to participate in the study for an additional 5 years. I agreed, but shortly after that, over the phone I was told my participation was no longer necessary, as the device had been approved.

I can't speak for all clinical trials, as Essure is the only clinical trial I've ever participated in, but I do know that others in this trial had eerily similar circumstances and experiences, although they were all in different states with different physicians.

Clinical trials for devices that will be approved as a Class III medical device need to have more oversight. If this is the FDA's gold standard, these trials need to be regulated or at least heavily monitored by an outside non-biased entity to ensure both proper patient care as well as study thoroughness. A check-and-balance system must be in place to keep trial participants as safe as possible and ensure the results are accurate. If struck by a terminal illness and this was a trial for a lifesaving device, I would have potentially exposed myself to greater risk. This is birth control and I was ill-informed. I implore the FDA to utilize its regulating authority and put some trial guidelines in place that will minimize mistakes like we have seen with Essure.

Fifteen years have passed since Essure was approved. As you will hear during Angie Firmalino's presentation, the FDA approval meeting for this product raised some serious questions. Seventeen years since I participated in this clinical trial, I am still asking how this happened. How was this ever approved? Where was the postmarket surveillance for this device? Fifteen years since approval, hundreds of known pregnancies, tens and thousands injured. Essure has been pulled from the market in every country but the U.S. How much is too much? At what point do the risks outweigh the benefits?

Thank you. Thank you for your time.

MR. CONWAY: Thank you very much.

Ms. Firmalino, if you could hold on one second.

Could I ask the tech folks, could you take the light and put it on the table? I don't think the speakers can see it. Just bear with us one second. Thank you.

(Pause.)

MR. CONWAY: Great. Thank you very much, I really appreciate it.

Our next speaker, who will be the speaker for slots number 4 and 5, will be Ms. Angie Firmalino, President of ASHES. Ms. Firmalino will also speak on behalf of Ms. Penelope Burau, who was unable to attend this meeting in person today.

Go right ahead.

MS. FIRMALINO: Thank you. My name is Angie Firmalino. I have no conflict of interest to disclose. I'm here to talk to you about my experience running a support group for women harmed by a medical device, leading an advocacy movement surrounding that device, and the 6 years I've wasted attempting to work with the FDA regarding the dangers of that device. The medical device I'm referring to is Essure, and I'm sure you've all heard of it. The support group now has over 35,000 members, mostly women harmed by the device. We also run 50 subgroups which have been broken down by U.S. state, debilitating medical condition, and Essure problems in other countries around the world. I think our initial flip from being a support group to becoming an advocacy movement came when we found and read the 2002 transcript of the FDA's premarket approval meeting for Essure.

The approval of Essure in 2002 was based on two non-randomized, non-blinded, prospective studies that lacked a comparator group and enrolled a total of 926 women. At the time of the PMA meeting, there were 281 women who had relied on Essure for 18 months, 149 women for 24 months, and 5 who had relied on Essure for 36 months. That was 435 of the original 926 clinical trial participants. What happened to the other 491 women in the trial, you might ask? That is a good question, and I'd love to know the honest answer, but I'm pretty confident I already do.

An article titled "Revisiting Essure Towards Safe and Effective Sterilization" was published in the *New England Journal of Medicine*. It summarizes those discrepancies and just happened to be released the night before the September 24th, 2015 FDA public hearing on Essure. Well, let me not get ahead of myself.

As we read through the PMA transcript, we listened to the manufacturer, Conceptus at the time, present their very impressive data on this new and revolutionary device, a device like no other on the market where a woman could be permanently sterilized in an office setting, the golden ticket that had been coveted for decades. As we arrived at the Advisory Panel members' questions and concerns, it was as though they were predicting what was going to happen in the real-world setting. The majority of those Panel members' questions and concerns went unanswered, and some were even turned into jokes. The frustration and anger of my team of administrators grew as we read on; the what ifs becoming jokes, the serious concerns lacking any plausible answers, and the sheer fact that there was such little data, such a small number of women followed for such a short period of time for a medical device that gets implanted into a young woman's body for her lifetime. The Panel members were not provided with the biocompatibility testing or with information regarding the PET fibers, because the manufacturer didn't want to make their packets too cumbersome.

I think the most frightening highlight of the transcript was when Dr. Seifer asked, "If in 5 years the failure rate looks greater than anyone expected, could there be some kind of contingency plan to follow that out for another X amount of time?" After some clarification of his question about what if things were to go horribly wrong, another Panel member, Dr. Roy, responded, "The private investigators would find each of us, bring us back here, and ask us why we approved this device." This statement was then followed by laughter and the chairman, Dr. Blanco, responding with "Okay, I think we better get to voting pretty

soon here." At that point we all realized we were guinea pigs and we were disposable pawns.

I called the video company that was listed on that transcript who recorded the live hearing, and my group requested, paid for, and bought the rights to the four DVD set video of the 2002 Essure PMA meeting.

We then initiated our first contact with the FDA. After several months of emails going back and forth, we were finally given the opportunity to have a phone call with the FDA officials on February 7th, 2014. The three FDA officials were Peper Long, Paula Silberberg, and Karen Jackler. They were very frank with us that they were not going to answer any questions or have a dialogue with us, that they were just going to provide us a platform for 1 hour so that we could present our information. So we had that phone call, and we presented as much information as we had at the time and nothing ever came of that call.

As our group grew and we continued to research, collect data, and conduct surveys, we put more pressure on the FDA, sending email after email, making phone calls and requests. We started to flood the media with our information on Essure. Finally, the FDA called for a public safety hearing on Essure and it was held on September 24th, 2015. Many of us attended the hearing, and we were given a few minutes each to speak. Our slideshows inconveniently weren't working, there seemed to be an immense amount of technical difficulties with our presentations, even though the new manufacturer, Bayer, and the FDA presenters' microphones and PowerPoints worked seamlessly. We were forced to stand at a small podium behind the line of red tape in a room packed with enough security to take down a small army. Maybe that's what they thought we were, a threat, a roomful of young and middle-aged women who just wanted to let the FDA know that we were sick and that we knew why: it was Essure.

Again, the Panel members had a multitude of questions for the manufacturer and for the FDA, most of which went unanswered yet again. Many of us in the audience behind the red tape could have answered those questions, but we were not allowed to speak during the Panel deliberations; our 3 minutes were up.

After much time and deliberation, the Panel members made their recommendations to the FDA. Eventually, the FDA came out with a draft guidance for a black box warning and a patient decision checklist. We asked to meet with the FDA once again. During that meeting we questioned why would it be a guidance and not a mandate? Benjamin Fisher told us that the mandate would take 2 years and they were trying to move things along a bit quicker. However, quick did not happen and after almost 14 months, the FDA issued their final guidance of the black box warning and patient checklist on October 31st, 2016.

Hundreds of women have joined our group, having been recently implanted with Essure after this guidance was issued. We surveyed them and 98% of those women were not informed of the black box warning nor were they required to review or initial the patient checklist. These women are being implanted without informed consent and I 100% blame the FDA for this situation. We told the FDA this was going to happen if they did not issue it as a mandate. We have also not seen any new brochures, pamphlets, handouts, or advertising from the manufacturer that include these new warnings.

We have 30 of the original Essure clinical trial participants in our group now, women that were in the trials in the United States, in the UK, in Australia. Even the doctor who read the clinical trials in Spain joined our group for a short period of time. We had shared this information with the FDA on numerous occasions. Yet, they have made no effort to speak to these women.

They have decided to let the manufacturer do a postmarket clinical study where they will implant 1,400 new women with Essure and compare them to 1,400 women who get a

tubal ligation. The results of that study will not be completed until 2023. In the meantime, they are leaving this dangerous device on the market while they wait for the results of this new safety study; the only market, I might add, where Essure remains because, as of September 18th, 2017, Essure was withdrawn from every other country in the world. This is an absolute outrage and a slap in the face to the tens of thousands of women who are already injured. There are so many existing databases where that information could've been collected and compared. Yet, they are going to put 2,800 women in a new trial and put 1,400 of them at risk with this device? What an absolute disgrace.

According to the FDA, Bayer has one patient currently enrolled in this new postmarket study. They have until 2020 to enroll all 2,400 women, which means the majority of them will yet again only be followed for a maximum of 36 months. In the real world we are seeing pregnancy, migration, perforation, expulsion, and autoimmune disease happen anywhere from 5 to 10 years after device placement. So the data that's going to be collected will yet again be woefully insufficient, as was the first clinical study. If the FDA cannot wrap their heads around that truth, then some heads need checking.

Thank you.

MR. CONWAY: Thank you very much.

I now ask Dr. Kara Haas from Johnson & Johnson.

DR. HAAS: Good afternoon. First of all, thank you to the Panel, Chair Conway, distinguished members, CDRH, Dr. Shuren. It's really a pleasure and privilege to be able to speak here this morning. My name is Kara Haas. I work for Johnson & Johnson in the medical device sector, in the regulatory affairs and policy section, and I'll be presenting today with my colleague Katherine Capperella, who leads a group in our Janssen organization for -- specifically related to patient engagement, she's our global patient engagement lead.

So for the last 75 years, Johnson & Johnson's credo is "Put Patients First." This goes beyond our credo; it's really a part of our culture. But as Elise stated earlier, over the last several years we really began to think about how do we engage patients to our total product life cycle and --

MR. CONWAY: Doctor, if I could just -- this is Paul. Hi.

DR. HAAS: Yeah.

MR. CONWAY: If you could just step closer to the microphone, that would be helpful.

DR. HAAS: Sure.

MR. CONWAY: That's great. Thank you.

DR. HAAS: Okay. Do you want me to start again or just keep going?

MR. CONWAY: Go ahead and keep going.

DR. HAAS: Okay. So as Elise Feliciano and Amy Loescher presented this morning, and they said over the last several years Johnson & Johnson has really been focusing on how we do things with the patient, not just for the patient, and the purpose of our comments today are really just to reiterate and echo a lot of the things that have been said, having heard the context over the last day and a half. But really, it's very important to us that we ensure that patients are along the journey with us.

MS. CAPPERELLA: Yeah. So as Kara stated, the slide we're looking at here is similar to CDRH's -- that really maps out different places along the continuum for engaging patients, and the reason we're showing this is to say that we firmly support and admire and thank you guys for taking the lead at FDA and getting patients involved in clinical trials. But also, we believe that the engagement -- and I think a lot of us are saying the same thing -- needs to happen even earlier, because we need to understand what it's like for patients to live with certain conditions, and from that experiential information it informs what data

we're collecting, what needs to be measured, and all of those things are happening so early in the process that they need to be captured so that we do have a good clinical trial and we're measuring what matters to patients.

So we applied the clinical trial focus, we think that is terrific; we all need to start somewhere and we can't lose sight of that fact before the clinical trial is critical, and also after. CDRH has done a lot of work on usability testing and providing guidance to make sure that instructions for use are clear, based on what we learn. And so the front end and the back end are really important in addition to the trial component.

We also believe that patient engagement should be measured and this just illustrates the fact that the clinical trial is one component and that we need to make sure the patients are providing input about the disease and also about what products need to be developed to meet unmet needs.

DR. HAAS: And really just to close out is, again, to thank the Committee and the FDA for the opportunity to participate this morning, to reiterate and reply to the three questions, at least two of the three questions, about some of the challenges and some of the activities we have taken to engage patients and overcome the challenges that happen in participating in clinical trials, and also to stress that engagement of patients also is going to require engagement of the other stakeholders, of the clinicians, of the whole ecosystem and communication that this is what's happening, because there's perceptions and misperceptions about what patient engagement means.

And lastly, it's really just stressing partnering with patients and vetting their voice in everything we do, delivering therapies that better meet patients' needs faster and if we can do so, hypothetically, the goal is, with all of us who are in this, better health for all patients. We'll also have more patients participate in clinical trials. We'll have devices that patients prefer on the market, patients are willing to take a look at the benefit and risk, and we'd

have improved health outcomes both on a patient level and a population level.

Thank you very much for this opportunity and again, thank you for the privilege of participating.

MR. CONWAY: Thank you.

Our next speak is Dr. Jennifer Horonjeff from Savvy Cooperative.

DR. HORONJEFF: Good afternoon. I'm Jennifer Horonjeff, and I'd like to thank the Committee for allowing me to speak with you here today, and I have nothing to disclose.

So I am a lifelong patient with chronic MS and founder of Savvy Cooperative, which is a patient co-op that helps to facilitate the collaboration between patients and researchers in healthcare innovations. Let's see how I navigate this here.

We believe that each stakeholder has a unique perspective and expertise to share when developing new innovations, all of which should be heard, considered, and included in the design and implementation of products and services. In no other industry would it be acceptable to create new products without consumer feedback. But because healthcare is more of a web of relationships rather than linear ones with perceived expertise, payers and users not necessarily being the same person, we forget that we need to know each perspective.

I'd like to share an excerpt from a 2009 qualitative study by Thompson et al. about patient involvement in research. I love this one. It says, "My boss is -- I wouldn't say that she's anti-patient. She isn't anti-it, but she holds reservations, and I think her reservations are the fact that she spent years training and studying to be a researcher and to get grips with the whole kind of research process, and these people have been bobbing around, taking pills and whatever, and claiming disability benefits for 5 years, and they are the ones coming in and suddenly they are the experts, and they have done no studying, no qualifications, and I think she feels a bit kind of like that's not right. Their experience

cannot outweigh my academic qualifications and knowledge."

So what I love about this excerpt is that the answer actually lies within the quote. The patient may be on disability and taking pills, but they are the only ones who know what that experience is like. We must not view this different perspective as lesser than and certainly not threatening. It should be perceived, valued, respected, and sought after as it complements the professional expertise and helps to contextualize it.

Personally, I've been on both sides of this equation as an academic researcher, human factors consultant, and I've heard patients -- professionals hypothesize about patients and their needs without ever talking with them. And as a patient I, of course, have been on the receiving end of poor design.

I'd like to share one quick story with you, a personal note, that as a master's student in ergonomics and biomechanics, part of my department was testing a new syringe. I wasn't part of the project but knew it was going to be spiffy because it was designed by a leading design firm in New York City and it was supposed to be easier to use. Several years later I got put on a medication that used this syringe and thought it was going to be an improvement over other syringes I have used in the past. To my dismay, I couldn't hold it properly at where I injected myself. And furthermore, because of its new size and shape, it no longer fit into the personal sharps container I had been provided by my doctor's office. So no matter how much I tried to jam it in and I actually tried to break it in two, it wouldn't fit into the opening. So all that innovation and it only made my patient experience more difficult. And this is a non-life threatening example of a medical device, and we've heard about others that have presented today about what it's like to have ones that are implanted.

During this experience years ago, I wondered if they had consulted any patients in the process, and if they did, was it just a tick box, or did they actually seek to understand

the full journey of how a patient interacts with the device? Patients don't think cross-sectionally. They think about the impact on their life as a whole. Here at the FDA we discuss safety and efficacy, but for patients, safety and efficacy are intertwined with ease of use, access, quality of life, and financial burden. These areas should be considered early and often through the development process.

I'd also like to add, with a push towards capturing the patient experience with PROs, that just because a patient reports something doesn't mean it matters to the patients. Patient-reported outcomes are different than patient-centered outcomes because patient-centered outcomes get to the heart of what matters to patients and what are meaningful to them and they're not limited to what can be captured on a PRO, but the only way to know that is to actually ask the patients themselves. Patients want their voices heard because collaboration not only leads to more meaningful and effective innovations, but also helps us foster a patient's own self-concept by giving them -- their experiences meaning and purpose and helping others in the future.

So, in closing, I challenge the FDA and all of us to consider how we can create a more supportive and collaborative environment so together, patients and professionals can work together to bring more patient-centered solutions to market faster.

Thank you very much for your time today.

MR. CONWAY: Thank you.

Our next speaker is Mr. Jack Mitchell, Director of Health Policy, National Center for Health Research.

MR. MITCHELL: Good afternoon, and thanks to the Panel for the opportunity to speak before you. I'm Jack Mitchell, and today I'm speaking on behalf of member organizations of the Patient, Consumer, and Public Health Coalition, which we help to lead. The coalition represents about two dozen nonprofit public health organizations, including

patient and consumer groups, which join together on issues of mutual importance to influence public policy.

In the context of patient engagement, an important step is for CDRH to educate patients about how medical devices are approved and monitored. Patients need education and training about medical device regulation such as the distinguished Advisory Panel members have received. Most patients, including the patient you heard from via videotape yesterday, are not aware of and do not understand the 510(k) device approval pathway. They're surprised to learn that devices are often approved based on a paucity of clinical evidence under 510(k)'s substantial equivalence standards.

They also do not generally know that lifesaving devices are held to different standards than prescription drugs. As Dr. Faris pointed out yesterday in his excellent presentation, for purposes of approval, devices are not drugs. Even when clinical trials are required, FDA often approves medical devices based on studies that have no or limited control groups.

Given the frequent lack of well-controlled clinical trials, patients are worried if the FDA's passive postmarket surveillance system is inadequate, often taking months or even years to identify and act upon a discernible pattern of device failure or harm to patients.

In addition, many patients who have been harmed by medical devices have complained that they were not told that their device was used off label or utilized in a medical indication which has not been approved by FDA. Surgeons, for example, routinely utilize off-label indications for surgical implants, including life-critical devices.

Your presence here today shows that CDRH has made progress in addressing patient-centric issues. Nevertheless, patients still often tell us they feel they are not listened to by FDA, especially if they are not affiliated with a group or aligned with a group funded by industry.

In a recent FDA panel that I attended, which focused on patients' role in drug development at the Agency, only one invited speaker was a patient and the rest were from industry, academia, or FDA. Dismayingly, when six patient advocates spoke as scheduled during the public comment period, which was at the end of the day, they were told they would have 2 minutes to speak rather than the 3 minutes earlier indicated. Two of the patients were cut off and asked to quickly summarize their remarks after speaking just 2 minutes. One patient had traveled from Minnesota at her own expense and waited all day to speak. She deserved a better reception, in our view.

FDA officials tell us that most patients want the FDA to approve medical device products more quickly. And certainly, industry is eager to get those patients in to the Agency to talk to FDA officials. However, most patients who are not dependent on industry financing, whether they have been harmed by a device or just want to share their stories about a need for treatment, are often not getting their voices heard. These patients don't read the *Federal Register*, they don't know how to write in to the FDA docket, and they often don't have the money to come in to FDA meetings, as Dr. Shuren noted yesterday, and he's indicated the Center is trying to find a solution to this vexing problem. Nevertheless, patients often ask me if it's worth their time and expense to come to the FDA given these limitations and the difficult logistics.

Patients also frequently complain it is difficult to get an in-person meeting with FDA officials. The Patient Health and Constituent Affairs Office has always been helpful and their staff has spoken to and interacted with our patient training groups. But on some occasions, it has taken a congressional staff intervention or prodding from our coalition members to get patient groups to obtain an audience with senior FDA officials. More routine outreach is needed to patients who are independent of industry influence or funding.

Another issue is that patient and consumer representatives on CDRH Advisory Panels, unlike those on FDA drug center representatives, cannot vote. Many are academics and nursing or social workers and some have been funded by device companies. These experts have important perspectives to share and should be included on Advisory Committees. But they are not patient/consumer representatives in a real sense. They should be joining the clinicians on the Panel, not replacing experienced patient advocates.

And, finally, patients should be aware of the Physician Payment Sunshine Act, legislation on which I worked as a Senate committee staffer. This easily accessible online database called Open Payments is maintained by the Centers for Medicare and Medicaid. It publicly lists medical device industry payments to doctors. Many surgeons have received hundreds of thousands, and in many cases, millions of dollars from medical device manufacturers. Patients should look at this database and know if their physician or surgeon has received such industry payments so they can judge for themselves whether or not these potential conflicts affect their medical care decision making.

Thank you.

MR. CONWAY: Thank you very much.

Our next speaker is Diana Zuckerman, President of the National Center for Health Research.

DR. ZUCKERMAN: I'm just trying of find out where the arrows are working, and that's not it. Oh, that one. Okay, sorry about that.

I'm Dr. Diana Zuckerman, and I'm President of the National Center for Health Research. Thanks for the opportunity to be here today. I have no conflicts of interest. We don't accept funding from device companies.

Thanks to an award from PCORI, we've spent the last couple of years training over 120 patients to understand clinical trials and so we've worked on that and learned a lot

from them, and also, we've been able to train them to understand trial design and not just clinical trials, but other kinds of scientific evidence of safety and effectiveness.

So what we found was that most of these patients, although they were advocates and had worked with other agencies, had not been engaged with the FDA. Many of them were desperate for treatments. Some of them had been harmed by treatments. Many had been recruited as patient advocates by nonprofit disease-specific groups and many had been recruited by industry. In fact, the vast majority of the patients who are engaged with FDA have been recruited by industry either directly or indirectly.

So, as you know, there are many different ways that patients can engage with the FDA and I'm going to focus on just a couple today, including participating by either being members of Advisory Committee meetings, members of Advisory Committees, or speaking during public comment period.

As has been mentioned, many of the patients who are engaged as patient representatives really aren't members of patient groups or consumer groups. Many of them are academic researchers and some of them even have connections to device companies.

One of the things that really concerns us is that in the past, these patient reps were able to and actually encouraged to speak to other patient groups before these Advisory Committee meetings, but in recent years they have been told they're not allowed to do that. They're supposed to be representing patients or consumers, and so we wonder how they can do that if they're not allowed to speak to groups beforehand. We understand they aren't allowed to provide information to these groups beforehand, but they should be able to listen to them and better represent them. So I encourage you to help with that.

Also, as has been mentioned many times, public comment speakers are limited to 2 to 3 minutes. They usually have to pay their own way if industry is not paying, and that can

easily come to over $200 per minute to speak at these meetings, and most people feel that that is not something that they can afford to do.

As you know, CDRH always gives a nice speech about respecting the patient and the public comment periods, but often they don't get to speak at a lectern. I'm pleased to be able to do that today. They are often behind a rope. Thank you, I'm not behind a rope today. And they are not asked questions. I think that's another thing that would be really important when people -- when patients speak during public comment periods, they've come at their own expense. It would be nice for them to feel that panel members want to know more and are interested to ask them questions. Often questions that really should be asked to patients are being asked to industry instead.

This thing is not working, I'm sorry. It has stopped. I think I pressed something inadvertently.

MR. CONWAY: No problem. Our tech is great.

DR. ZUCKERMAN: Okay, thank you. Thanks very much.

I won't go into the written requests for comments, but of course most patients don't read the *Federal Register*, they don't know about this opportunity to make written comments, which at least would be free, they wouldn't have to travel to do it, but they don't have that opportunity very often.

And just to mention that when comments were asked for electroconvulsive shock therapy devices, thousands of patients did respond. Seventy-nine percent of them expressed concerns about the standards for letting those products on the market and yet CDRH decided in the opposite direction, to ignore those concerns.

So in talking to patients, I'll just say that many of them who have been harmed tell us they feel dissed, they feel that their experiences aren't taken as seriously as patients who are happy with a new product. They feel that when they talk about what happened to

them, it's treated as an anecdote instead of as clinical evidence. And yet, when it's -- when patients are happy with a new device or a drug, it's treated as clinical evidence.

And as you know, microphones can be shut off, I'll try not to make that happen to me, but I've seen patients crying about a loved one, who died as a result of being harmed by a medical product, being shut off in the middle of their tears.

Here's just one example of a child who was given Infuse, a device. Their face is swollen. That is not a fat baby, that is a baby with a swollen -- a swelling in their brain and their head. Two years later another patient had exactly the same thing happen. Patients begged FDA to put out a warning and instead of putting out a warning that was clear, saying Infuse causes this problem, the warning said certain recombinant proteins and synthetics can cause a problem with patients under 18. So we ask for clearer warnings -- thank you. Sorry about the beeping. And just for clearer warnings for products when problems have been found, so that patients can understand them, as well as doctors.

And I just have some pictures of some of the patients who have been harmed, who were not able to come today, but who asked me to show their faces to let you know that they're sorry they can't be here, but they either were too ill to come or couldn't afford to come.

And thank you very much for everything that you're doing and I hope that you will be listening to these harmed patients and make sure their voices are heard.

Thank you.

MR. CONWAY: Thank you.

Speakers 10 and 11 will be Ms. Linda L. Radach, charter member of the Washington Advocates for Patient Safety. Ms. Radach will also speak on behalf of Ms. Beverly Pennington, who is unable to attend this meeting in person today.

MS. RADACH: Good afternoon. I'm Linda Radach, and I'm speaking on behalf of

Beverly Jane Pennington as well as myself. I'm here as a patient and as a representative for the Patient Safety Action Network affiliated with Consumer Union's Safe Patient Project. CU did pay for my transportation and lodging. I am also here as a representative of the independent voice of the USA Patient Network, which has been formed out of our training with the National Center for Health Research.

My journey with these issues began in 2006 when I had bilateral hip replacements. I had been told by my doctor that the devices were newly approved by the FDA, that they would last 20 years, maybe my lifetime. I later learned that the devices were not cleared for market until 3 years after implanting and removal of the devices from my body. The early failure of those first implants created a cascade of events that have resulted in six hip replacements. I have been diagnosed with metallosis and cobalt toxicity, which is responsible for the hardening of my heart walls. I live with daily pain, poor mobility, a loss of work, and a future that is compromised by the damages from the use of untested, illegally used devices.

I'm speaking today from my own experience and those of other patients who I've talked with over the last 11 years, as well as the research that I have done to understand how FDA operates.

First, I do appreciate the fact that FDA has formed the Patient Engagement Advisory Committee and that you're trying to seek patient perspectives. It is our thoughts, our experiences, and ideas that should be the loudest, most important voice for you. On the patient continuum there's a wide range of experience and needs creating quite different levels of risk tolerance. Yet it seems there is not equity in terms of whose voice is being heard. It does seem that FDA is influenced by patients who report good outcomes regardless of what the data reveals.

It seems as though the patients who are desperate for treatments for rare or chronic

diseases are solicited for their opinions and perspective more often than the harmed patient. In fact, there are thousands and thousands of patients who have been harmed. In fact, right now there are probably at least 200,000 patients at risk for cobalt toxicity due to the use of dissimilar metals in hip implants. And yet when we come here we feel as though our voices are ricocheting off of empty space, as our experience and attitudes and actions we receive from the listeners convey a message that we are complainers and our stories are referred to as anecdotes, isolated case reports or unsubstantiated opinions.

In truth, our stories of harm have the deepest and most profound lessons from which industry and FDA can learn how to better understand the minds, needs, desires, benefits of patients that they're hoping to serve.

Personally, I'm not interested in something coming fast, and most of the patients I know are not interested in speed. They're interested in safety and effectiveness, period. I didn't get hip replacements to have a greater problem. It was supposed to solve a problem and it didn't.

So what are the challenges in medical device clinical trials and possible solutions? From my perspective, and those that I have talked with, patients need to trust the processes enough to feel safe to participate. Patient reticence to engage is a consequence of systems which do not appear safe. Patients need to know that they're listened to and that their input and experience is received and validated. As I said, patients expect devices to have the FDA stamp of approval on them that they will be safe and effective, but it seems every other day there's a new headline talking about problems with failed medical devices. Whether reports about joint replacements, breast implants, or the cost to see a mess of failed cardiac devices, it is impossible to be blind to the truth that medical devices and the processes by which they come to market are not adequate.

We would recommend establishing an Advisory Panel that is of, by, and for patients

like the one that CDER has. Make sure those patients do not have ties to companies that make devices or nonprofit organizations that receive funding from device companies. Patients provide the single most powerful source of real-world evidence and we can tell you what is an acceptable risk tolerance, but it will vary from group to group. We can tell you what's important to us and the devices that we receive or what we would like in a trial, what works, what doesn't.

Please don't assume that we only have an elementary level of education and I'm not capable of understanding complex studies and issues. I came into this out of need and I have learned a tremendous amount and I think I can stand my ground. There's nothing further from the truth that patients can't understand.

There is, unfortunately, abundant evidence of the lack of safety and effectiveness of devices already trialed on the market. According to Device Events, there are 157 Class III devices currently on the market. In the first 7 months of this year alone, Class III devices have likely contributed to the death of 3,614 patients and resulted in over 86,000 injuries. Since 2008 there has been a six-fold increase in death and injury reports submitted to the FDA and you wonder why we don't trust it.

Even the *Journal of the American Medical Association* recently did a review of clinical trials used to support the high-risk medical modifications, and this is the conclusion of their study: "Among clinical studies used to support FDA approval of high-risk medical device modifications, fewer than half were randomized, blinded, or controlled, and most primary outcomes were based on surrogate endpoints." These findings, according to *JAMA*, suggests that the quality of studies and data evaluated should be included -- should be improved. And perhaps there would be if patients were listened to earlier. Designing a clinical trial for a device has its challenges, to be sure. A prospective patient may wonder who's going to get to the less-than-stellar hip implant. Cardiac patients may wonder who's

going to undergo surgery without receiving a device at all. Immoral, unethical. There are other ways.

Researchers and patients alike could be concerned about the potential use of sham treatments in controlled studies. There are other possibilities which do not negatively expose patients to the risk of surgery, which would be far preferable, such as comparisons between a well-functioning device that's already on the market or a surgical procedure that doesn't require a device.

If you want to encourage patient participation, full disclosure is a necessity. Patients need to be asked, listened to, and honored for their input. We should be provided with protection of Investigational Device Exemption status.

The disconnect for me in this discussion is that since there are less than 2% of medical devices proven safe and effective, the vast majority reach the market through the 510(k) process. And though the FDA describes 510(k) as ensuring safety and effectiveness, we agree with the 2011 Institute of Medicine report which says that it is not possible to identify a device as safe and effective based on substantial equivalence. They are two different measures. Patients are not being protected when so few scientific controlled studies are conducted. And once on the market through the 510(k) process, the ability of FDA to respond is restricted by lack of tracking and severe lack of reporting.

I could go on, but the truth is patients perceive too much risk without benefit to participate. And me, I perceive too much to even undergo another joint replacement. The burden has been shifted to industry -- from industry to patients.

In closing, never in my wildest imagination did I dream that I would one day be here at a public hearing of a federal agency. When I scheduled my hip replacement, it was inconceivable to me that I would be harmed as a result of regulatory failure. Yet here I am having had my life and my health turned on its head by devices which were never tested for

safety and effectiveness. I'm not alone, I'm not an outlier, I am not an anecdote, I am not insignificant, and I am not mistaken. I am a patient whose voice needs to be heard but is rarely heard at CDRH or their Advisory Committee meetings. It is time for the FDA and for industry to do the right thing because it's the right thing to do. It's time for FDA to use the authority that it has to protect patients, not facilitate easy, quick access to market for device makers.

You asked what patients think. Listen to us. Do it as the right thing for our health. Make your actions match the words. Protect the public health with truly safe and effective devices. It might even save your life some day.

Thank you.

MR. CONWAY: Thank you very much.

(Applause.)

MR. CONWAY: Our next speaker is Ms. Bel Broadley, a member of the Parkinson's Foundation/Parkinson's Advocates in Research. Ms. Broadley will also read a written comment submitted to the Committee earlier from the Parkinson's Foundation once she has concluded.

MS. BROADLEY: Good afternoon. My name is Bel Broadley. I'm here representing the Parkinson's Foundation. I am being paid for both my -- for my lodging and travel.

My husband, Michael Young, is a Parkinson's patient and he brings me here today. We represent the community of people with Parkinson's disease and their care partners. Mike and I are research advocates with the Parkinson's Foundation. The Parkinson's Foundation makes life better for people with Parkinson's by improving care and advancing research towards a cure. Most importantly, they empower people with PD and care partners like Mike and me to be equal players in the research and care that improves our lives.

The next slide.

The Parkinson's Foundation has trained Mike and myself through their Parkinson's Advocates in Research program, otherwise known as PAIR. Through the PAIR program we trained specifically in the research process and how to represent the community perspective in our work with industry, academia, and government. We help prioritize research, improve studies, and influence stakeholders so that research better addresses the unmet needs of the community. Ultimately, this helps clinical trials move forward more quickly and effectively.

Most recently in my role with the foundations, I have reviewed grants from the Department of Defense Parkinson's research program and I'm right now in the process of doing that again. And I work with the foundations to provide feedback to an industry partner on a study protocol. This included providing insights on the preferred devices to be used as drug delivery systems. Nationwide, Parkinson's Foundation research advocates have shared community perspectives on preferred devices, device design, and usability and benefit-risk feedback.

This slide lists devices that people with Parkinson's may use now or in the near future. Mike and I have personal experience with some of these devices. In 2014, Mike underwent brain surgery to insert a deep brain stimulator system. This was a tested device that improved his base level of motor function significantly. Michael has also provided end-user feedback on a prototype device in two successive years. The second prototype had benefited immensely from patient input, particularly ease of use and reduced size.

Sharing our personal experiences with researchers and engineers, we include the practical everyday habits we developed to live with such devices. We report our experiences with things like initial cost, insurance considerations, repairs and maintenance, restocking medications and supplies and often, restrictions imposed by such devices.

Bringing such factors forward to researchers and engineers will lead to development of better living solutions for the Parkinson's community.

As Parkinson's Foundation research advocates, we engage early and often in the research process. We would like the Patient Engagement Advisory Committee to urge FDA to utilize patient advocates like us at each step of the device development process.

We believe it is important to get benefit-risk insights as early as possible, even during device conception, before time is spent developing prototypes and executing trials. We also believe patient advocates can provide important insights at critical junctions or pre-Investigational Device Exemption meetings. We encourage the Patient Engagement Advisory Committee to support FDA's efforts to create guidance for industry as to how our perspectives can and should be integrated into these processes.

I have to let you know, on a personal note, that it was only after I became a patient advocate that I truly became engaged in research. It was that mere thought that I was being listened to and understood the connection between research and final design. Thank you very much for your time.

Now I'm going to change to the letter from the -- this letter is addressed to Letise Williams of the FDA from Jim Beck, Chief Scientific Officer of the Parkinson's Foundation.

"Dear Ms. Williams: The Parkinson's Foundation appreciates the opportunity to comment on the U.S. Food and Drug Administration's deliberations involving the regulation of medical devices and use by their patients. The Parkinson's Foundation is a nonprofit organization that makes life better for people with Parkinson's disease by improving care and advancing research to a cure. Our foundation understands the importance of prioritizing and acting on the perspective of people living with a disease.

"Since 2008 our groundbreaking patient advocacy program, Parkinson's Advocates in Research, has trained 288 people with Parkinson's disease and care partners, whom we call

research advocates, to engage in research and represent the perspective of the Parkinson's community with government, academia, and industry."

I must say that we -- they reach out to engage people who have a true interest in advocacy before they come to the training. There is no extraneous qualification in terms of scientific or other background, educational background.

"For example, in recent years our research advocates have provided feedback to AbbVie with Duopa, UCB Neupro, NeuroDerm investigational drug ND0612 recently acquired by Mitsubishi Tanabe, and Biogen investigational drug BIIB054. Both investigational drugs have delivery mechanisms that involve devices.

"Research advocates have shared community perspectives on preferred devices, perspectives on device design and usability and benefit-risk reward.

"As the FDA considers the regulation of medical devices and their use by patients, we support the proposed objectives of (1) better understanding challenges for patients in medical device clinical trials, and (2) better understanding how patient input and the engagement is being used to overcome these challenges.

"To achieve these objectives, the Parkinson's Foundation recommends the following:

"(1) Encourage sponsors to utilize designs such as the benefit-risk framework for medical device clinical trials early and often in the research and development process, including when considering study design. For example, sham surgery has been used in Parkinson's clinical trials and is controversial within the Parkinson's patient community. A better understanding of community perspectives on benefit-risk would help inform the use of this type of trial design. We also support the recent guidance on benefit-risk factors in influencing device availability, compliance, and enforcement decisions and encourages its use for Parkinson's devices.

"(2) Include people with Parkinson's throughout all stages of the

development of new devices. We recommend working with patients through the expertise of nonprofits with strong patient engagement programs. We also recommend asking questions of patients that broadly represent the community, questions such as: If multiple devices could deliver a drug effectively through different delivery mechanisms at different locations on the body, which location and type of device would you prefer?

"(3) Develop the processes for incorporating patient input into pre-investigational new device meetings. We support FDA's upcoming work to provide clear guidance to industry as to how to effectively work with patients.

"Sincerely, James C. Beck, Ph.D., Chief Scientific Officer."

Thanks for your time.

MR. CONWAY: Thank you very much.

Our next speaker is Mr. Paul Madden, Managing Director of Adult Initiatives, American Diabetes Association.

MR. MADDEN: Thank you very much. I'm absolutely honored to be here today. Patient engagement, absolutely, in my short 55-plus years of living with Type 1 diabetes. And as I speak about my life, I'm speaking about the lives of half a million or more people with diabetes. I'm a psychologist by training, was the first full-time psychologist at Joslin and Harvard Medical School. So my focus has always been "how are you doing" and a lot of that "how are you doing, how are you doing with this technology, which is robust?"

The first insulin pumps, 1977, '78, I wore those pumps. They lasted 5 days. Compared to the pump I wear today, it was horrible. But we made the pumps better because a group of assertive patients from the East Coast, from the West Coast, from the North and the South, spoke up with very little direction and just said this is what we need. So I applaud FDA for this warm welcome to say, "Patients, we need your voice."

So much has been said yesterday and today that I, as an individual -- this is the public

session. ADA has not guided me on what I will say today, I want everyone to hear that. And most groups that have paid my salary have never been able to tell me what to say when I'm in front of federal groups or certification groups. I'm pleased to report that.

In diabetes, there are unparalleled advances in diabetes, especially the technologies. You and I, we are getting close, close to balancing blood sugars as if one did not have diabetes. That means a reduction of the serious complications which do not need to occur.

Now I put my science hat on and I will tell you that the bulk of the scientists in the diabetes world and with enthusiastic -- and I heard again and again, knowledgeable, bright patients and their loved ones. We realize that we people with diabetes are really on the border of getting, with these new advances that are -- in the last several years, more rapid advances have happened in technology than occurred in my first 49 years of life with diabetes. So it's exciting but a little frightening, too, because we have to learn how to use these things.

NCDs, highlighted by diabetes in the United States, are the leading cause of new poverty in the United States. New poverty. It doesn't need to be that way. Health, lifestyle choices, and more balanced diabetes will save significant healthcare dollars and expenses because it will increase productivity, quality and the quantity of life. Why do I emphasize the business side of this? People have already talked about the science beautifully. I will not reiterate that, but I believe in what I have been hearing today. But as a citizen of this country, my country has to invest in me and everyone else out there who has some added challenges of living a bold, robust life. I appreciate that the FDA has that focus for us, so I thank you for that.

And the payoff from a financial standpoint -- I know us in medicine don't like to talk about it's going to pay off, but it does pay off with more balanced conditions as we slow down the development of devastating conditions which really strip away our minds, our

bodies, our ability to be more independent.

This study shows that patient engagement does work. What you see and what you hear and what you see and hear and what you do is when you learn most about the products for the scientists, the companies, for FDA, and us, the patients. So thank you for embracing that.

Keeping your population, us U.S. citizens, healthier absolutely will pay off, not just for the quality of lives but everything. We have to look at all of us challenged by something as a proper investment as citizens of this beautiful country. And I think all too often we're looked at as only an expense. I appreciate the FDA -- I know it's not a money discussion, but you do talk about our quality of lives and you do that.

Pancreas is involved. I thank you from the bottom of my pancreas. Thank you so much.

(Laughter.)

MR. CONWAY: Thank you very much, Mr. Madden.

Our next speaker is Ms. Elisabeth George, Head of Global Regulation and -- I apologize -- and Studies. Can you tell me what the organization is, is it Philips?

MS. GEORGE: Yes, it's Philips.

MR. CONWAY: Okay, my apologies. Thank you.

MS. GEORGE: No problem. Good afternoon. Elisabeth George. I'm the Head of Global Regulations and Standards with Philips. My employer did pay for me to come here today and all my expenses. I am here today as a consumer, as a patient, as a caregiver, as well as in my role at Philips.

Philips is a health and wellness company with a broad range of products. We have products in the consumer area, our Sonicare toothbrush that probably everybody has, hopefully. We have health products, we have software applications that are on people's

phones, and then we have a lot of medical products ranging from MRI, x-ray, defibrillators, etc.

This inaugural meeting has been fantastic, and it's wonderful to hear everybody's voice. Like Dr. Blackburne, I am one of the industry reps for PEAC. I get the fun when we decide to have the postmarket discussions, so I'll be sitting up there with all of you guys and I'm looking forward to that. I am very excited about all the accomplishments this week and the future of this group.

I think it is a little bit sad, however, that we didn't have more people here to be able to hear and to see the huge amount of effort that everybody in this room has taken, the amount of passion. But I do think that, based on the level of the FDA and patient engagement, I know that there's going to be a great deal of valuable learning, successful practices, and innovative ideas that will get disseminated.

As the FDA has reminded us, patients are the heart of what we all do, so I want to thank you and give that thanks to all of you, the Panel, for the time that you've spent; the FDA for the inordinate amount of time that you've spent getting us here today; all of the presenters and the audience, including those who spoke with a lot of deep passion and powerful messages in this afternoon's Open Public Hearing.

Thank you very much.

MR. CONWAY: Thank you very much.

At this point I'm going to ask Dr. Tarver to come on up.

DR. TARVER: So I just want to thank everyone who spoke today and yesterday during the Open Public Hearing. We really do appreciate your courage and your frankness in expressing your experience with medical devices and the challenges that you've had. We will take the comments that you all expressed during this Open Public Hearing session and integrate that into the changes that we explore with clinical trials and how to make them

more patient-centric and patient-friendly.

Thank you.

MR. CONWAY: At this point I'd like to ask anybody on the Committee if they have any questions for the folks who spoke today at the public hearing.

Go right ahead, Doctor.

DR. BLACKBURNE: Hi. Rose Blackburne, the Industry Representative.

I had a question from earlier today, and it was touched on a little bit, but I'd like to maybe tease it out a bit more, about patient engagement with discussions with payers as part of a life cycle of the product development and then the payer discussions coming at some point, and do you engage patients in that to get their input and, as final end users, how these products are going to be paid for? Do you include them in those discussions? And for any of our industry representatives that would like to maybe touch that.

MR. CONWAY: Actually, Doc, we aren't going on this. We'll have time to pull in the speakers from this morning.

DR. BLACKBURNE: Do it later, okay.

MR. CONWAY: This is actually for speakers that spoke --

DR. BLACKBURNE: I'm sorry.

MR. CONWAY: -- this afternoon.

Having said that, I personally have a question for two of our guests, but I'll go ahead and defer to you, Dr. Parker.

DR. PARKER: Monica Parker.

There were two speakers that came up with a term, and it kind of bothered me a little bit because it sounded -- sounds awful, actually. Not necessarily being a surgeon, I'm not familiar with sham treatments. Can somebody help me a little bit more? I mean, we're not really allowed to use medications. You know, there is either a medication that gives

you the usual treatment and you give somebody a placebo, but I've never heard sham medicine, so I'm unfamiliar with sham treatments and devices and surgical devices. Can somebody --

MS. RADACH: It is an alarming phrase, isn't it?

DR. PARKER: Yes.

MS. RADACH: And it was alarming to me. I wish I could tell you -- cite the exact study, but I do not have access to it. I was told about it from a very reputable source, but there was a clinical study that was done with a cardiac device in which half of the patients went through surgery and received no treatment and the other half were given a cardiac device. That is as unethical and immoral as anybody can imagine, and that's what has been termed a sham treatment. It's not really there, and the patients don't know that. That's unnecessary risk.

MR. CONWAY: Okay, after Ms. Radach, if Ms. Broadley could go ahead and answer the doctor's question.

MS. BROADLEY: Essentially, part of double-blinding in the case of Parkinson's patients, when they did the first of the deep brain stimulators, which really is inserting things in the brain, that half of the cohort had simple abrasions done to -- they were not allowing the patient to know that they were not receiving the device and they bore holes in the skull but not performing the implantation. And apparently, the scientific community is okay with that, but there's a lot of resistance in terms of the patients, or there's kind of a little controversy about that type of blinding.

DR. PARKER: Thank you.

MR. CONWAY: Great. I'm going to go to Mr. Downs, and then we'll go to Amye and then we'll go to Deborah.

MR. DOWNS: Fred Downs.

A question that I have to the first presenter, the patient who had a number of -- she had a number of problems over years. I was just curious, did you have access to some kind of support group, through the internet or whatever, who were having similar problems? Were you able to come together and discuss those unusual problems?

MS. HUDAK: At the time, no, I had no support group, nobody had heard of the device. I didn't have the support of my physicians because they weren't familiar with it. In fact, my primary physician had in my medical records that I had a tubal ligation, and I said well, why did you put that? And he goes, because you started telling me about some metal coils and I thought you were crazy. So no, there was no support group available. I didn't find a support group until 2012. That was 12 years after I was implanted. So no, at the time there was nothing; I was alone.

MR. DOWNS: Okay. I asked the question because it may be indicative of other areas where patients are having difficulties and no one to go to, so thank you.

MS. HUDAK: Yeah, thank you.

MR. CONWAY: Amye, go right ahead.

MS. LEONG: First of all, my thanks to all of the speakers for your presentations, in particular to those who really spoke of personal harms. I know personally of the rancor you have to go through each time you relive what it is you put down on paper in order to stand before any group, besides this group, to speak that. So the question is actually in recognition of elocuting those harms that you experienced, or others like you experienced, and then asking our friends at the FDA, what is the current standard of process for anybody who feels that they have been harmed or have received some sort of symptom or treatment that is inconsistent with what was originally told to them? So I'd like to get an FDA perspective on that.

And, Paul, I turn it back to you to direct maybe Michelle to give us that idea. I think

it's important to lay that out properly. Thank you.

DR. TARVER: So as you alluded to, in a clinical trial, sometimes the harms are not known and it is an investigational device. I'm sorry, the harms may not be known because it is an investigational device. If patients experience harms, the process by which the Investigational Device Exemption, which a lot of devices are studied under, there's a reporting requirement that is part of that. There is also, in the postmarket setting, opportunities to report. The patients and providers or reporters make a report through the voluntary MedWatch system, and manufacturers are required reporters through the MedWatch system.

MR. CONWAY: Thank you.

MS. LEONG: Thank you.

MR. CONWAY: Coming back over to you, Deborah, you were going to ask --

MS. CORNWALL: Deborah Cornwall.

I wanted to pursue both the -- and I think there is a connection here, both Kim's example of the implant of a device that had not yet been approved, which to me sounds like it was an illegal device of some sort, and the comment about sham surgery that Gail introduced. I think it was Gail.

And my question is, it's a double question that builds on the question that you just answered, Michelle, which is what is the responsibility of the FDA in those situations? For instance, the comment that it's okay with the scientific community that you can have a hole drilled in your head but nothing implanted. You know, I'd like to know what is the -- is there a position that the FDA takes as their responsibility? But also, how does the FDA know whether they are being told the truth when, in fact, there is information that is being provided as part of the clinical study or by the manufacturer related to either the IDE or the postmarket problems? How do you know that you are, in fact, hearing about those

situations, and what is the responsibility of the FDA related to those kinds of situations?

DR. TARVER: Michelle Tarver.

So the FDA does review protocols that are submitted for certain submissions prior to initiation of the studies, depending on the risk of the device. The study usually and almost always has to actually be evaluated by an institutional review board, so there are parties involved in determining the ethical conduct of the trial.

MS. CORNWALL: So the IRB is, in fact, authorizing the sham surgery?

DR. TARVER: The IRB reviews all protocols, and they usually have patients that sit on their boards as well that review the protocols prior to making the decision.

MS. CORNWALL: And how do you know that you're getting accurate feedback either from the clinical trial or from the postmarket introduction? How do you know that you are learning of the kinds of problems that we heard today?

DR. TARVER: So before I answer that question, I do want to add one point on to -- I think the question that Amye had asked about how do -- what are the recourses for reporting the bad consequences that patients may experience while in a trial, and informed consent forms are supposed to have information that gives you a number and someone to call to report an experience that is less than favorable. And the IRB does review those adverse outcomes that happen within a trial.

In terms of the quality of the data that we receive, we do have statisticians that look at the data, and we look for patterns in terms of the accuracy, validity, and the associations that we would expect to see with the data. So there is a rigorous investigation of the data that we do receive.

MS. CORNWALL: But it's investigation of the data you do receive.

DR. TARVER: That is correct.

MS. CORNWALL: So if it is not reported and if you learn later of a situation in which,

whether it's the IRB or the scientific investigators, and you learn of a situation in which it was not reported but a problem exists, is there any action that is warranted on the part of the FDA or any other government agency?

DR. TARVER: So I think this -- this is Michelle Tarver again.

I think this is a perfect opportunity of something for this Panel to discuss, which are ways that we can engage in the pre- and the postmarket phase for medical devices and how we can design protocols that address those concerns.

MS. CORNWALL: Thank you, that's what I was trying to find out.

MR. CONWAY: Thank you, Michelle.

If there's one thing I could say about that, I think what we're going to learn in this process is that there are probably going to be some issues that are a matter of law, a matter of regulation, and a matter of process. And I think, as we deliberate as a committee and we listen to not only public testimony, but as we listen to experts from industry and investors and from other organizations that are out there, we should always be thinking in terms of what is law, what is regulation, and what is process. And I think through that lens (1) we can learn a lot, but (2) I think it will better inform some of the issues that we look at going forward.

But I wanted to step back, if there's not another question from a colleague, and ask two folks who had testified earlier a couple of questions. (1) I don't know if -- I didn't see -- oh. Hi, Dr. Zuckerman. Do you mind coming forward for a second? So this is a question from me. Just so that I have this right, and so my Committee colleagues have it right in their minds, as well, am I correct in characterizing your statement to be something along this line -- and if I'm not, feel free to correct it. I'm going to base it on -- I'm fairly easy and I can get bounced around.

If a patient participates in an activity at the invitation of FDA or if a patient applies

through a process to participate in an FDA forum, an advisory board or anything like that of the vehicles that FDA makes available, and somewhere in their history as a patient they have participated, one, because they either wanted to or because they did not have the means to, if they participated at some point in their journey in some type of industry-sponsored event or had travel or had lodging paid for, is it your suggestion that somehow if that patient participates in a federal government forum or body, that somehow their testimony or participation is less relevant or less legitimate than someone who has never had that history in their patient journey?

DR. ZUCKERMAN: No. That isn't what I intended to say. Let me clarify. There are patients who are recruited and trained by industry and they have -- they're basically getting all of their information about clinical trials or about safety data or about efficacy data or effectiveness data from the training that they're getting from industry, and I just -- and that training can be very good in certain ways, but it's going to be biased in other ways. And in our experience working with a lot of different groups, some of which accept industry funding and some don't, and working with a lot of patients, some of whom have received money and training from industry and others that haven't, you know, a lot of individual differences. But some people are really so closely aligned with industry that they don't -- that they're not open to other views.

And so I guess what I'm asking for you all -- and I know nothing about your backgrounds that -- to be sure to be listening to those independent voices and not just the voices of people who have received funding from industry or are very -- are getting all their training either directly from industry or from nonprofit organizations that are funded primarily by industry.

And I can say, just to say that my dad worked for Johnson & Johnson his whole life. I'm not against industry. But, you know, different people have different points of view. By

the way, my father thought FDA was way too strict on every issue. I don't happen to feel that way. But, you know, you have these different views, and it comes from the experiences that you have and the people who train you and what they've taught you. So what we find is that the patients who have been harmed are not being funded by industry. Those are the voices that aren't getting heard much because those are not the voices that industry is recruiting and encouraging to engage with the FDA. Is that --

MR. CONWAY: Yeah. No, actually, it's an appropriate clarification, and I appreciate it. And I also liked asking you a question.

(Off microphone comment.)

MR. CONWAY: Sure, go right ahead.

MS. CHAUHAN: I appreciate your concerns. I just want to be clear that you're aware that the FDA vets the patient representatives very carefully for those kinds of ties and that it does its own training program, a yearly intensive training and then monthly and bimonthly training.

DR. ZUCKERMAN: Yes, we're aware of that. Let me say that our center also gets to vote. I don't know how many others vote, but we do get to vote on candidates --

MS. CHAUHAN: Yes.

DR. ZUCKERMAN: -- for patient or consumer reps on various CDRH and CDER panels. And so we see what their qualifications and credentials are, and they vary a lot, and we absolutely have been asked to vote on candidates who are inventors who have invented devices and yet are asking to be patient or consumer representatives on CDRH Advisory Panels, which to me doesn't make sense. To me, they -- it's fine to have them be the industry rep, but we don't think they should be the patient or consumer rep if they have those ties, and the fact that they're candidates who are being voted on suggests to me that they've gone through some kind of vetting process that considers them acceptable.

MS. CHAUHAN: So you're basically asking the FDA to be more vigilant --

DR. ZUCKERMAN: Yes.

MS. CHAUHAN: -- in vetting the patient rep for the panels?

DR. ZUCKERMAN: Right. And let me say that some of the candidates we've seen, their whole -- you know, they are patients or they have community service. Some of them, you know, have been volunteers for the Boy Scouts. I don't consider that a qualification to be a consumer rep, and I don't think -- I mean, it's fine to be a patient and not have ties to patient groups, but I do think that it's good to have a track record of representing people other than yourself.

MS. CHAUHAN: Thank you.

DR. ZUCKERMAN: Thanks.

MR. CONWAY: Thank you.

One last question, and then we'll take a brief break. If Mr. Madden could come back up, I'd appreciate it. This is my question for you.

MR. MADDEN: Please.

MR. CONWAY: I appreciated your testimony, everybody's testimony. You wear several different hats.

MR. MADDEN: Um-hum.

MR. CONWAY: Putting your hat on as a patient, I want to ask you this question because what I'm trying to drive into is this issue of -- and I think it's directly relevant for where this Committee may go in the future in terms of asking questions.

MR. MADDEN: Um-hum.

MR. CONWAY: It's along the line of mutual exclusivity, I even say, but in your experience as a patient, you were very clear in your statement up front that in your career your comments have not been directed by payment or reimbursement.

MR. MADDEN: Um-hum, correct.

MR. CONWAY: Can you just give me your reflection, based on the several hats that you wear, one as a patient and one as an academic, how deep do you think that issue runs? And in your own life, have you ever felt conflicted between an association with a patient organization or with someone that paid for your expenses and the information that you would relay to an official body of the government, federal, state?

MR. MADDEN: I have never felt conflicted whatsoever. I represent myself and I represent -- and truly about 50,000 people that I have -- who have diabetes and their -- plus their family members that I always represent. As the Joslin and the Harvard Medical School will remember, as I'm still on their voluntary leadership council, I am a quiet diplomat who can be very stern and says -- I don't argue much. I just say no. And then I tell them the science that I think is better. So I've never felt conflicted. Others may listen to me and feel I might be, but I've never had anyone say that in my 45-year career.

MR. CONWAY: Okay, thank you. You've answered my question.

MR. MADDEN: Yeah, thanks.

MR. CONWAY: I'd like to say thank you for all of our guests. I think that -- and as an Advisory Committee, but I think with any time the federal government engages citizens and especially, I think, it's unique for FDA or CMS when they engage patients, this is actually one of the most important parts of the meeting. And I'll offer a personal comment here, but it's in the context of what we've talked about and the testimony that's been provided. And I'll do that by way of a story, not an anecdote, and I'll make that point in a second.

I knew a patient, proud service in World War II in the Navy and in the Marine Corps, served his country for about 30 years, fighting the Cold War, retires and passes away due to a medical error. So that person was not an anecdote; that was my father.

And one suggestion that I would make to you as you consider, Committee, is this:

that there are many different walks of life represented on this Committee. It took a great deal for the federal government and for the FDA to assemble us here. But as I said yesterday at the start of this, and I said it for a very particular reason, that our charge is to be fair and unbiased when we listen. And we're listening.

That's why we're here. But I'd also like to assure those who had the courage and used their own means and took their time in that great investment, which I understand fully, to be here, that the passion, the personal interest, which is a good thing, especially when you're a patient, and that your concern for those who will come after you is not missed on this Committee, regardless of the people and their backgrounds here. Every single one of us has been touched, and the compartments that sometimes people will assign, you know, they're easy to do because it's easier to make an intellectual deduction from that. But sometimes they just don't apply, and I think when it comes to things like healthcare and health journey and those who have been in your life and that you've lost, it's just different, and we're here to make a difference.

So in the context of that, I'd like to go ahead and take a brief 15-minute break, and then we're going to come back, and as a committee, we're going to talk through some of these issues that were laid out on the agenda today. And before we conclude, we'll have interaction with the FDA and start to come up, I think, with where we are on some of these questions and how it might inform us going forward.

But again, for those who had the courage to be here today and to speak to us, we deeply respect you. Thank you.

(Off the record at 2:49 p.m.)

(On the record at 3:10 p.m.)

MR. CONWAY: Okay, folks, it's 3:10 right now, and I'm going to go ahead and call the meeting back to order, and we'll proceed with committee discussions of questions and

recommendations.

If there's one thing I could just point out quickly with the audience, and again, I appreciate you staying with us. As a reminder -- and this is a matter of decorum and process, which is important, and avoiding the appearance of conflict of interest, if our public could stay back in that section and keep the Committee up here, just separation so it doesn't look confused, we'd appreciate that.

The other thing I'd like to say is this, I should've said it at the beginning, in terms of when the Committee has listened to different folks testify, I think you've heard sometimes people clap on the Committee and sometimes people have not. I want to just give this assurance that, ideally, we would refrain from that, but I don't want anyone to take away from this that somebody favored another person over another person or a testimony over a testimony. I think what you're looking at is a Committee that's coming up to full running speed, and it's all good intention, but I don't want somebody to leave after 2 days and feel as though they were either disrespected or were not listened to or a judgment was made. That's not the case, okay?

Having said that, at this time we're going to go ahead and focus on our discussion questions from the FDA. Committee members, just so you know, copies of the questions are in your folders. I'd ask that each committee member identify him or herself each time that you speak to help out the transcriptionist. I'd also like to remind members of the Committee that this is a general issue meeting, and reference to specific products and firms should not be included in this discussion.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Committee Chair. And I'd like to thank you for observing that over the past 2 days.

I'll ask the FDA to please read the questions. Ms. Miller, you may approach the lectern or have a seat.

DR. MILLER: Hi. Good afternoon, everyone. I'm Dr. Lisa Miller from CDRH, and I will be presenting questions from the FDA to the Committee. There are a total of five questions. Let us begin.

No. 1: What opportunities and barriers (perceived or real) might patients and patient groups experience when attempting to collaborate with industry on the design of clinical trials?

a. How might these opportunities be expanded? And

b. How might those barriers be overcome?

MR. CONWAY: So here's what we're going to do, folks, as a committee. I'll ask you each to give your viewpoints on this, and then at the end of this, we'll try to summarize them, understanding the fact that we are on the second day and that our answers may not be perfect. Our consensus will reflect, and our comments will reflect, that which we've heard and which we've brought to the table at this point.

So would somebody like to begin?

Amye.

MS. LEONG: First of all, I want to recognize the nature and depth of the comments that we have received over the last 2 days, and I want to thank those who presented them to us. There were many items that were mentioned, that were clarified, reiterated, emphasized, deemphasized, but I think in total, all of the comments were substantive, that's how I'm taking it and certainly will create much more thought for us.

I also want to preface my comment for this particular question with that I will have more to say about this much later, simply because to ask us now in one question at a time is not going to capture my complete thought on this whole entity of patient engagement in

clinical trials.

With having said that, with respect to Question No. 1, I think it's really important that everybody be on the same page, that the transparency of some sort of framework, optimally established by PEAC or the FDA or CDRH, would be very, very helpful, but certainly to have a framework so that patients, patient groups, patient advocate leaders, industry, academicians, trialists, fully understand the nature and the benefits of coming together, first of all, and secondly, how might best we do that and from what entity this is being laid out.

So my first response to this, it would be setting up some sort of framework that all stakeholders have an opportunity to input into, that a nonpartisan body take a look at, that again, stakeholders have a relook at everything, and ultimately some sort of guidance that then everyone is fully transparent about.

Thank you.

MR. CONWAY: Great, thanks.

Yeah, go right ahead, Cynthia.

MS. CHAUHAN: Cynthia Chauhan.

I'm going to respond in terms of how I see the FDA's role in facilitating expansion of the opportunities and overcoming of the barriers. I know that the FDA works closely with industry when they're developing the trials and gives a lot of guidance and input. So I think as part of that, in working with industry on trial development, the FDA should encourage industry to have patient involvement from conception of the idea, and should ask these questions of industry when they are ready to bring it to the FDA: How did you engage patients in the design and development of the concept and trial? If you did not, what is your reasoning? And second, that they should include in their presentation planning on how results will be shared with patients. I think this is where the FDA can have a significant

impact on getting patients involved early. If we ask the question, then they are more likely to focus on what they need to think about and answer this.

So thank you.

MR. CONWAY: Other committee members?

Bennet.

MR. DUNLAP: I think that the opportunities of engaging with patients are significant, and if you'll allow me a second, I will use a recent success of FDA and patient communities and industry as an example, and that's the artificial pancreas. Kind of working backwards in time, the FDA was just recognized with a Sammy Award, which is a recognition of excellence in government service for their work in this area, and I think what's really significant is that over the past 6 or 7 years, by engaging with patients, FDA got a better appreciation of the risks of living with Type 1 diabetes. It's a dangerous disease. As Paul Madden said, insulin is not the safest thing in the world to be putting into someone, and I'll tell you that as someone that had a 7-year-old that was injecting herself, it's a pretty frightening thing. But FDA worked with patients to understand our perceptions of what would be risks that we would accept and risks that we wanted, and I am confident that that helped them accelerate bringing that useful device to the public, and that is a case study of the opportunities. I think the barriers are what was expressed from some of the groups yesterday, and that is that there isn't really a roadmap of how to do that. And I think that it is really useful to try to build that roadmap, look at that successful case study as an example, and the wonderful input that we had from those round tables yesterday; that was the most amazing process I have ever seen at an FDA hearing, and I've been coming here for 5 or 6 years.

MR. CONWAY: Thank you.

Go ahead, Doc.

DR. BLACKBURNE: Good afternoon. Rose Blackburne.

I think one of the opportunities uncovered this afternoon, and it was very compelling, was the journey of the safety collection data. So I really appreciate and thank this afternoon's presenters about their struggles post-procedure and sharing their stories. That was very difficult. So how can we better capture their struggles and finding truth and validation or recognition about what they went through with the studies? A different way to collect safety data is another category. Around complications. How do we help them find the answers? To Dr. Tarver's comment, a lot of it is unknown, there's risk, but how do we help them kind of navigate the unknown a lot better?

MR. CONWAY: Dr. Seelman.

DR. SEELMAN: Yeah, this is Kate Seelman.

I have about three different responses on this one. The first one is to follow Dr. Blackburne. I've used the adverse effects FDA database, and I think that for consumers or patients to have more confidence in the FDA, that there might need to be other pathways to handle adverse effects information and the adverse effects database, however, whatever it's called, the FDA database is certainly useful, but I don't think it's sufficient, especially after the discussion today. So that's number one.

Number two, there would be -- I asked the question twice to various people, and I do appreciate the presentations so much. What is value added from the consumer or the patient advocate? And it seems to me that some kind of framework or checklist or factors list would help us along the line here. And certainly for medical devices, one of the -- after pain management and medical symptoms, usability, quality of life has not come up. Activities of daily living has not come up. Cultural variables and the importance of cultural variables has come up, but it has to continue to come up. I mean, some kind of checklist is what -- what is so valuable about our input, and eventually moving to some quantification

of what this is.

And, finally, I've been uncomfortable with what seems to be the lack of representation of people with disabilities in clinical trials. And I mean, for example, I'm a good example of a pretty healthy person with a disability and I mean, people who -- across the board, mobility, death, blind, cognitive, and especially people with developmental disabilities have -- we haven't heard very much about meeting their needs. So I think those are my points for right now.

Thank you very much.

MR. CONWAY: Great, thank you.

Mr. Downs.

MR. DOWNS: Fred Downs.

What does the patient want versus what does industry want and does the patient know how to describe what they want? I think that's a barrier. I think ignorance, maybe that's not the -- well, ignorance is probably a pretty good word. What is the process? Does the patient, as part of the trial group -- the professionals are the scientists, the doctors, the researchers. The patient is the only who's not really a professional, and so how does one overcome that? And this sense of mistrust from industry, what are they driving at? What is it they want and what inhibits the working relationship between industry, the patient, and the researchers, and people involved with it? And communication, that's my other note here. Also a lack of guidelines. So is there a book that someone could open up and say okay, here's my role as a patient, a researcher, the questions, the weaknesses, the strengths, here's what I need to be doing and here's why I'm part of this trial? And that would be different, perhaps, for each research project. But if, sort of, guidelines could be opened up for a patient, they'll certainly follow and the rest of the team, too, they're all going to have their own individual tracks that they want to follow. So keeping them all

together on the same path as they begin to move down to develop the design of the clinical trial, I think, is important.

MR. CONWAY: Great, thank you.

Dr. Parker.

DR. PARKER: Monica Parker.

Opportunities and barriers. I think that one of the best things or worse things, I guess, that I heard is that from the personal testimonies, many of the people weren't aware that they had an opportunity to interface with industry at all, and consistent with what some of my other colleagues have said, they didn't -- they weren't aware of how they could do that. So we need to make it more accessible or ability to interact with industry a little bit more available and maybe one of the ways -- the easiest ways to do that is to make sure that these opportunities are conveyed to the different advocacy groups because I'm sure they will get somebody here to testify and participate.

MR. CONWAY: Okay, thank you.

Suzie.

MS. SCHRANDT: Hi. Suz Schrandt.

I think my comments sort of follow on some of my colleagues' thoughts about maybe the need for a framework or a checklist. What I'm focused on is a couple of qualities that we would want to make sure are embedded in anything like that that we might want to produce. One quality is to just really sort of hold ourselves accountable to be focused upstream, that it's never too early to start engagement and you actually miss opportunities. One of the very first presentations yesterday, there was a slide with some really thoughtful questions one might ask as they're evaluating the patient engagement in a clinical trial design, and one of the question was are the right patients going to be enrolled in the study? So you can imagine that a more upstream question would be were there patients involved

in defining the exclusion and inclusion criteria? Or do the patients understand the risks and benefits? The more upstream question is did patients help articulate what a benefit means and what a risk means? So just really pushing to start that bar up front because I think it saves time and energy, and it starts that process sort of the right way.

The other piece is to make it continuous, and that's both engaging the people who are in the trial, but also something like a patient advisory board. We don't want it to be transactional. I think we really want an iterative, continuous process with lots of touch points to all the patients involved.

My last point is -- I can't shut off the lawyer part of my brain, and so this one piece that I'm really kind of stuck on is about the concerns around proprietary issues, and I understand that fear, that mistrust, that if an industry partner is sort of sharing this information that in and of itself has value, you want to make sure that the patients understand and sort of respect that it is proprietary.

I have two points, though. One is almost a direct counter to that, which is that I can't say enough how much value that the patients bring, and so I think we miss that when we focus only on the monetary value of what the companies are offering. But the other piece is I think we really -- as an operating premise across all of patient engagement, we want to learn from patient engagement as it's happening. And so to the extent we executed a nondisclosure agreement or a confidentiality agreement as part of any engagement activity, let's make sure that's not a barrier to a company sharing what they learned from the engagement. So not about the -- I'm not even talking about results of the trial. I'm talking about results of having patients engaged. So we had fewer trial amendment -- you know, protocol amendments. We had better recruitment. That's not necessarily about the results; it's about a product of the engagement. So let's be very mindful that anything we do to protect proprietary information isn't a bar to sharing what

we're learning about the engagement.

MR. CONWAY: Okay, great. Thanks.

Go ahead, Deborah.

MS. CORNWALL: Deborah Cornwall.

I will try to make my scribbles coherent. I think that there is a broader issue at play here as we look at this question, but also the other questions that Lisa is going to be going through, that we have on our agenda, and that issue is patients are people. Patients are not sources of statistics, they are not collections of medical information, they are not inputs to a medical database somewhere in the cloud. They are people.

And I think that as we talk about opportunities and barriers for greater engagement, everybody involved -- you know, a lot of what we heard this afternoon, not a lot, but some of the pieces of testimony that we heard this afternoon had to do with trust and had to do with what is the role of the FDA in relation to industry and in relation patients, i.e., people? And I think that there is a broader cultural, psychological, and educational issue that needs to be addressed; that can't be resolved this afternoon. My personal feeling is that you have given us far more insight than we could've imagined coming into this meeting. And it is encouraging that this meeting is taking place, and I know the commitment of the people who are sitting around this table with me, and those who are not at the table, is very strong to addressing these issues.

But I think that what we're really dealing with is finding a way to build a mindset that recognizes that the FDA, industry, the patient community, and the public at large need to have some more common goals in this entire process, and I think there is a broad education, with a capital E, process and culture change process needed to start understanding that everybody playing this game -- it's not a game, but everybody in this exercise has perhaps different stakes, different goals, different expectations and hopes for

what will come out of the process, and I think the role of this group in answering these questions needs to be to find ways to bring those goals together so that we are working on a more shared agenda that does more trust-building across all of those bodies and all of those parties who are engaged.

So whether it's the scientists or representatives of industry, representatives of patient groups, individuals, the general public, or the staff of the FDA, I think, you know, there is going to be a need for finding ways, and those won't be defined this afternoon, finding ways to build that shared understanding and some shared goals that will then allow us building on any common rungs about a framework, that will then allow us to create a kind of framework that we can start building on to address not only this question but many of the questions that have come up over the last 2 days.

So, you know, some of it is information sharing, some of it is building more understanding, but I think that underlying it all is a combination of culture change, psychology, and education and finding ways to have a dialogue that addresses all three of those issues in ways that we can address these questions with the attention that they really deserve.

MR. CONWAY: Thank you.

Any other comments on this?

(No response.)

MR. CONWAY: And then I'll offer my own, and then I'll move to summarize the question.

In listening over the past 2 days, a couple of things occur to me. Every party that's involved in this process is responsible. So I don't believe that the onus rests on government alone. I think a tremendous amount of the onus rests on industry. I think a tremendous amount of the onus is owned by patients and patient advocacy organizations. And it goes

to many of the issues that Deborah has talked about.

I think in terms of educating people and changing a mindset, if we have this many Americans, and the demographics points in this direction for these number of diseases, and the promise of technology and innovation is here and tracking along that, and if the end goal is to create improvements in accessibility to devices that allow people to reach their aspirations, then that requires a change in how we think together, all parties. So I don't think you can isolate it to one stakeholder alone in the process.

Specifically, I think many of the things that have been identified here are either barriers or opportunities depending on how you look at it. I think that a huge amount of concern has to track back to the original FDA mission and the purpose of the PEAC, which is to take a look and to assist the FDA in their efforts to protect health and safety, but also to offer a candid set of opinions and advice to FDA and to the Commissioner about how we might best improve things. And I think that, literally, the comments from the round tables and the public comments today, I think there's enough content there that gives you the guardrails, gives you the action items, and then also sets us up looking forward to start to identify things like roadmap, educational tools, and that type of thing.

One last personal comment: I agree with my fellow committee members that there's a huge amount of information, but also that our answers today should be caveated in the sense that we haven't seen all of the information that's come out of the past 2 days, and taking that and processing it over time, I think you'll get a better sense of exactly where we are.

Having said that, I think there's some things that we could probably say that, generally, from a consensus standpoint, we're going in that direction of. At the outset, I would say that the comments that Deborah made are very important, that it's going to involve things that go beyond FDA in terms of how we take a look at this as a country and as

citizens and as patients, as industry, as investors, and as government.

Getting into the specifics, I think there's general agreement around the table that some type of framework that demystifies the process -- in terms of who does that, we can sort that out, but demystifies the process to make certain that it's absolutely clear to patients what their risk is, where they go for information, the ease and accessibility of being able to participate, to make certain that barriers such as income, economic background, disparities, racial disparities, different audiences that we're not penetrating into are addressed, that it's absolutely clear and in plain language for everybody on how to do it.

I think the suggestion that Dr. Seelman made on the specifics of what should be involved in a roadmap are very important, and I'll let her comments stand on that, they're fairly detailed. And I think the idea of having some type of checklist also, in terms of those things that we need to include, are important. And some of those that were elaborated on are important. Usability, quality of life, aspirational issues, cultural variance, I think those are important.

Also, as a summary comment, I think that the points that Mr. Downs made are very important as well, in terms of making certain that we take into account the understandability of everything that we're doing, even in the roadmap type of approach to it.

And then the final point that, I think, in terms of summary that's important is the pointing of further upstream, because I think we need to take a look at the standpoint -- and I know our focus is not cost, but I'm not talking about financial cost, I'm talking about the cost on patient lives, loss of income, disability, lack of opportunity, inability to travel, inability to live. When you take a look at the human cost, the further upstream you go, I think it's incredibly important. What that looks like and how you model that, I think we actually might be able to take a stab at that.

But in summary -- and I put that forward tentatively, but if my committee members want to whack me, feel free. But I hope that answers the question or provides an answer in summary to Question No. 1, Dr. Tarver.

DR. TARVER: Yes, it does. Thank you.

MR. CONWAY: Great. With no dissent, if we could go ahead and move to Question No. 2.

DR. MILLER: Yes, thank you.

No. 2: In general, what aspects of the trial design contribute to enrollment and participant retention challenges? What are methods to better address these challenges? Please consider the following in your discussion: informed consent, randomization, outcomes meaningful to patients, frequency and number of visits, assessments performed, and study duration.

MR. CONWAY: So we'll go to Dr. Parker, and then we'll come over here to Cynthia.

DR. PARKER: Monica Parker.

One of the things that kind of struck me, and it was in part of the testimony for several people, was to make sure that the language that was used, for example, to obtain informed consent or even to explain the study, is made to be something that was pretty plain, plain language, easy to understand. I heard no stronger than a sixth or eighth grade, and that's what we hear in journalism; you should never talk much above an eighth grade level. So I think that language has to a lot to do with getting people -- in terms of understanding things, being clear with language that people can -- speaking in language that people can understand. Literacy.

MR. CONWAY: Sorry, Cynthia.

MS. CHAUHAN: No, that's fine. Informed consents are a problem, I believe. They often scare patients because they're often written to protect the company more than to

inform the patient. With devices, as you were talking, it came to me, why not have illustrations in the informed consent? I think that would help people to understand. I know the eighth grade level is ideal. It is becoming harder and harder to do that as medicine becomes more complex. So I think they are a barrier, I think there are things that can be done to make them better.

I think randomization is a barrier to patients; it is very scary to patients. I would like for us to think in terms -- I've been in some studies where I was randomized, I've been in some studies where they were double-blind crossovers. I liked the double-blind crossover because then you're all on kind of an equal playing field. It means that for part of the study I get whatever, for part of the study I don't get whatever, and I don't know which way it's going. And the lady from the Parkinson's group talked about a double-blind crossover in Parkinson's where they just turned the device off and on. So that might be an underutilized way to get people into trials instead of randomization.

Outcomes being meaningful to patients is very important. That will sometimes work over the problems with the consent and the randomization.

Patients tend to go into trials from a very altruistic point, and so that's very important.

Frequency and number of visits and assessments performed. I think that's an open thing that depends very highly on how it is presented to the patients. I like trials that have calendars that they give to patients. The calendar is close to an illustration, it's an explicit laid-out statement of what you do, when you do it, how long it takes to do it, and that gives patients good information that, I think, helps for these not to be barriers.

Study duration: I think that's open, again. It relates to how carefully you explain to the patient what's going on and why it's taking so long. And I think it's really important for patients to know that when I finish my participation in the study, that does not mean the

study is finished. And so to give patients both those pieces of information. Your participation will be 12 weeks, unless something happens that it's shorter, but the study, because we want -- I'm making up numbers -- 1,200 patients, will go on for 3 years and then we have time after that to put the information and figure out what we learned in the study. To be more transparent about that will help study duration, I believe, not be a barrier to patients.

Yeah, thank you.

MR. CONWAY: Great, thank you.

I'm going to go to Mr. Dunlap.

MR. DUNLAP: Bennet Dunlap.

I just want to make one comment about outcomes meaningful to patients. I'm very optimistic in my outlook on life, so I always think about what are those good outcomes. I think it was extremely eloquently presented today that there are outcomes that are extremely meaningful that are negative outcomes, and there needs to be part of the informed consent process that's crystal clear how to report those in ways that are not influenced by a commercial activity.

MR. CONWAY: Great, thank you.

Doc.

DR. BLACKBURNE: Rose Blackburne.

I would take a step back, and we touched on this all through our discussions yesterday and today, on the topic of educating patients, family members, educating the public about clinical trials, and then as a part of that, reintroducing the terms and defining informed consent, and all of these different aspects of the trial again and again and again and again. I think the iterative process of understanding will evolve as the patient moves along in the trial process from informed consent to data, data readout. So that's one thing.

In terms of informed consent, some of the things that I've raised with patients and protocol writers is e-consent, electronic consent, but also a video explaining it along with text. And, again, we talked about common everyday language. I've helped to write informed consents, and certainly, you're supposed to be at an eighth grade level. You know, when I would read them, it was like, wow, I don't even understand that. So really understanding that when we say eighth, we use that grade cutoff, but meaningful to patients that are going to be in the study and what does that mean. And, again, explaining what randomization means again when you randomize, when you've been randomized, when they're at their different study visits. And then what the outcomes mean as they go along and, you know, why are we doing -- iterating why we're doing each step.

I think the frequency and numbers of visits applies. You know, how can we reduce the burden? Is it after hours, is it the home care, blood draws, telemedicine, using all the technology that we have available and really determining from study design, do we actually -- and this was raised, do we need all of these visits and why? And then explaining -- maybe giving patients a summary of each visit. So today you had X, Y, and Z done. This is what that means. You did your PRO assessment, this is what it means. They may think someone asked them some questions. This is actually an instrument used for the study and this is why we're doing it. So maybe after each study visit, giving them a summary of what happened this day, this time, so that they have it and they can review it with -- when they get home, when they're more relaxed with family members and they can review it as they go along. And then the same for the assessments performed.

And I think Cynthia touched on, you know, explaining what study duration means compared to study participation and study assessments and when will the data be coming and all those things around duration. So just the iterative process of educating and reeducating and clarifying, and this is what it means now and this is what it meant, so that

there's just a lot of information defined and distilled for better understanding.

MR. CONWAY: Okay, we're going to go Dr. Seelman, and then we're going to go over to Dr. Parker and then come back to Deborah.

DR. SEELMAN: Yeah, I was kind of surprised in this question, and maybe it doesn't belong here, but we're a patient engagement panel, and I will tell you that, from my experience, mobile phones are a great way internationally, nationally, and locally for patients to be engaged and consumers to be engaged and maybe we need more studies about the efficacy and protections of privacy. I don't know. But it seems to me that that technology would impact on the design right at the beginning. And, you know, we heard at least one case study yesterday, and I'm sure that there are many, and certainly I've been involved with some. So I would think having that technology and knowing that we can do international trials easily engaged using this technology as well as local and national. So that was one thought, and I was surprised it's not here somewhere.

And then I was thinking of my mother. My mother, next to the priest, but the doctor, but the doctor was always somebody with great respect and great awe. And then I think, though, my graduate students and we have -- I have, in school at Pitt, a course that was very participatory in terms of disability. So a lot of consumers were invited in to work with me and with my students, but getting the consumers to feel comfortable in a university was a big problem, they were very intimidated. And so the comfort level of the consumer and patient engagement is, I think, very, very related to how much assistance we're going to give them. Dr. Blackburne talked about the informed consent and if they're people like us, I mean, we're all patients, consumers, and others. Even a protocol of comfort, how you make people, you know, feel a little more comfortable with the situation, because this is not any more than consumers coming in to universities after 50 years not being there or never having been there, it's not a comfortable situation for them. So those

are mine.

MR. CONWAY: Great. Thank you.

Dr. Parker.

Okay, no problem.

Deborah.

MS. CORNWALL: Okay, I just had two comments, one of them related to Mr. Dunlap's remark about the informed consent process, and I think it connects also with the outcomes meaningful to patients. I think what we've heard today says that we need to learn more and reevaluate the process for reporting of adverse events, and in order for the patient population to feel as though they are being heard, there may be a need for multiple channels, multiple simultaneous channels, to ensure that the negative events are arriving somewhere that will get the kind of attention that says we know you exist, we know it's an issue, and that will provoke follow-up.

The other thing I wanted to remark on was a comment made by Dr. Seel [sic] about engagement and telephones. I love technology when it works, and I guess I have to just ask what do we mean when we talk about engaging the patient, because I think one of the challenges that we have, and it actually relates to the first question, is that the medical system today does not allow a lot of time for interaction between the patient and the medical provider.

And I think one of the things that we need to think about as we are not only looking at how we engage patients, but also how we design trials in ways that they feel engaged, involved, and heard is to figure out what elements of the process can be handled technologically without any -- without either leaving out any population like technology averse people -- it may be a function of age, it may not, but also finding ways to ensure that they are feeling as though they are getting the support. And a piece of what I'm getting at,

again, is the human support from whether it's the scientific providers or the medical providers who are running the trial.

MR. CONWAY: Great, thank you.

Amye.

MS. LEONG: I was trying not to answer this question, but I have to step in. Thank you so much. And I absolutely agree with what my fellow panelists have said. I think when it comes to development of trial design, we have to really think about what we said, what we heard and said yesterday and today, that it's important to engage patients from the very beginning in the ideation stage. Now, is it the patient that's taking the survey? Is it the patient advocate leader who's going to be part of a steering committee? Is it someone who knows the community? Is it a faith-based leader who has knowledge of community and can really be an assist in this whole development of a trial design? Or it could be one or all or even more than what I have said. But in each of the bulleted areas, it tells me that it's got to be done from the very beginning, from the very start.

Now, where I have an issue and where I have been involved in the issue is where when you have a patient advocate across the table from a trialist who has a different perspective and a different goal than the patient or the patient advocate and you have two heads butting against one another, who wins? I can tell you, at least in the cases I've been in, it's always the trialist because it's that person's study funded by industry or whomever, foundations or whomever, with a very certain specificity of intent and potential outcomes. So by the time that a faith-based person, leader, is for example, invited to be a part of a steering group, talking about each of these areas, informed consent and whatnot and providing a community base very much representing the type of community we want to have engaged, it's too late. It's even too late there.

And then what happens when it's one person against another person or two people

against two? Usually what happens is the patient loses out in terms of their opinion because the Ph.D. or the M.D. or the person who funded the study has a different purpose in mind. What do we do then?

So I think that we, as a PEAC, have some issues to deal with when there are some deeply embedded historical processes that have succeeded the concept of patient engagement at the real, original beginnings. How do we resolve the voice of the patient as it relates to the recruitment and retention and engagement when a study design has already been developed? I cannot answer that, but I hope that our Committee will as we move this forward.

Thank you.

MR. CONWAY: Thanks, Amye.

Mr. Downs.

MR. DOWNS: Fred Downs.

Just to add a family involvement, that whole process from an informed consent on through, I think is important.

MR. CONWAY: Great, thank you.

Barring any other comments, I'll go ahead and give my own opinion. I think a lot has been put on the record here, but there are two things that come to mind. One is what I would put under ease of use or ease of understanding. And I think one of the things that contributes to better enrollment and retention in the study is how you approach the education module, not just for the patient and some of them have been mentioned here, but I think the influencers in somebody's life, if it's a caregiver, if it's a faith leader in the community, that's important because if you were to take a look at it from a public policy side, a grassroots national side, those are the influencers that you want because they can disseminate information, but also they're a trusted source of information.

However, having said that, there are other places that I think education is needed, and I would say that that's at the medical level. If we're going to ask the medical community to become more involved in steering their patients or encouraging their patients -- and steering has no negative connotation, but if we view them as an influencer to try to get more people involved, then it must be understandable to doctors that they're seeing. So if a patient is considering going into a clinical trial for something that they see specialists for, but the bridge person for that or the point of influence is the GP, I don't think you can put the GP on the hook for knowing the details of it if the language is convoluted and not interesting to them or doesn't catch their eye or is not published in a medium that they see regularly.

The other area that I would comment on is this issue of technology and I think there are a lot of different places to look to see where the applications of technology have great benefit. Again, pooling from another life in terms of national policy and grassroots, I think there have been some very outstanding examples in the past 10, 12 years where cell phone technology has been used to actually engage people in very complex national issues, substantively. There are other examples where it's not substantive. But I think you can use it as an engagement tool, but that has to be at the front end, it's very expensive.

And there's also components of it, and it was touched on a bit here, but the use of gaming technology, and I'm not talking about, you know, some kind of crazy video game; it's to further engagement, there's a whole science and technology to that. I know that the FDA has had an interest in that in different sectors, but there's a great deal of investment that's put into that in the private sector that I think could be looked at.

One caveat to that, and that is something that was touched on here, and this is a personal experience and personal opinion. I think the more highly reliant you are on technology, you must also have an aggressive outreach campaign, again, through the modes

of influence in somebody's life, because you cannot isolate yourself into technology zones where people have the money and the means to buy phones or to be near the internet or have a connection because you can leave a whole population out. That's personal experience when you're trying to engage dialysis patients and others. People assume, well, everybody in a dialysis chair may have a phone. In fact, a lot of people don't. They don't even have transport. But you want them interested and you want folks like that engaged, especially the people that are further upstream. Those are my personal opinions about that.

If I can make a set of summary comments: I think this question in particular is another one of those where we would say that there's a great deal of information that we, as a committee, bring to this. And so in answering the question, Dr. Tarver, I would put out two caveats: (1) We're giving you our initial consensus on this; (2) We're going to be interested in taking a look at the transcript and also the round tables and, again, at the public hearing testimony today. But I think this is one of those questions that sets itself up for what are best practices and also, in reflection, what are some of the worst practices.

If you take a look from the aspect of the past several days, and I think many of the comments here kind of reflect what we've heard from people saying hey, I didn't know X and I didn't know Y, and that goes directly to the issue of how well informed they were up front and how understandable that information was.

I think the issue of randomization, and I think the issues of having something that's predictable to a patient and transparent, the calendar that Cynthia raised and some other folks have raised, that there's date certainty so you can actually plan your life because not every patient aspires to have their life run around a clinical trial. We'd rather make the clinical trial run around our life and our aspirations.

This issue of demystifying the process, I think that's also in terms of the plain

language. But I think, even further, there are fear factors, there's the mystery of it all, and then the basic human question of -- and again, Cynthia touched on this and others have, the basic question of if I am going to put my time and my effort and my life in service to a clinical trial, "To what end" has to be the question that is answered at each point in the spectrum and "To what end" can be answered even in the easiest way of this is where we are in the process now, this is how many people are involved, and this is when you can reasonably expect an update." Not that complicated and respectful, but I think that that, especially on the issue of retention, would go a long way.

If I've missed anything, I turn to my folks and say go ahead, but I hope that that is an accurate summary of what our folks have said and is responsive to the question.

DR. TARVER: Yes, it is. Thank you.

MR. CONWAY: Thank you.

If we could go ahead and move on to the third question.

DR. MILLER: Thank you.

No. 3: What do you believe to be the most effective means of recruiting and enrolling patients? Should recruitment and enrollment approaches be customized to better meet the needs of the following:

a. Rare disease populations (e.g., flexible inclusion and exclusion criteria);
b. Different racial/ethnic/socioeconomic/religious/gender and sexual orientation groups (e.g., sociocultural sensitivities and economic barriers);
c. Different age groups (e.g. pediatric and elderly assent/consent processes); and
d. Mentally or physically disabled groups (e.g., visit burdens)?

MR. CONWAY: Great.

Dr. Parker.

DR. PARKER: I think this was my favorite question, and based on the testimony we heard here today, there were three groups that I was particularly interested in and liked to hear their comments. But before I say that, we have a whole government-funded entity that has studied this very thing and that's the PCORI institute.

The things that I heard that had greater resonance for me, and I don't think a lot of researchers do, is they said partnering with yes, okay, primary care. So I'm going to get to throw that one out here, partner with the doctors, the -- whether they're primary care doctors or specialty doctors within the communities where their patients are coming from, but strategic partners, professional associations, advocacy groups. And the gentleman that talked about pediatric research, using patient registries as sources of patients who would be amenable to participating in clinical research studies, I thought those were fantastic things, they're sitting right here in our face, and it's sort of like we have a whole group that's worked on this, so we don't have to really reinvent the wheel.

The other thing that I thought that was very important was when it comes to special groups, in qualitative research we have this term called purposive sampling, which means you go to where the people are that fit the criteria that you're looking for. So if you're looking for certain ethnic groups, you go to where those ethnic groups reside, where they live, where they work, and who are the doctors, etc., that are treating those people, that's where you go to find them.

Over here, when it talks about different age groups, I think the same argument applies, but the thing that -- because I am a woman of color and because there is not enough diversity in the scientific workforce, I support anything we can do to increase the number of minority scientists and yes, women are a minority, women of color, it doesn't really matter, different ethnicities, but gender is also -- makes you an underrepresented group. So I think that having ethnic and gender concordance with respect to investigators

going to specific communities, I think that's a very important thing and I think it's frequently overlooked. And if I had to put on my bullhorn to talk to the NIH, it's sort of like you need to start funding people who look a little different.

MR. CONWAY: Thank you.

Suzie.

MS. SCHRANDT: Hi. Suz Schrandt.

I think it's a great -- about PCORI and I'll actually -- I'll get to that in a minute. I think this question is challenging to me because I think it's a little bit risky to answer it as written. I feel like the best ways to recruit or retain -- I could answer No. 4 the same way. The best ways to recruit patients are the ways that patients tell us they want to be recruited. So to put that differently, ask the patient. And so instead of offering tactics, I would want to put forward that as the best practice, and it's specifically important within these subpopulations because everyone's going to look different. If you want to do a pediatric study in asthma, get together a panel of 10 kids with asthma and talk to them about recruitment. Once you've got them in the study or even before, ask them how they -- what will keep them in the study. And I'll put my PCORI hat on for a minute. I remember being on phone calls and talking with investigators and saying -- you know, they were saying what do we do with the patients? And I would say ask the patients, just ask the patients. And so I can't say that enough times. But with respect to -- I think you're exactly right, Dr. Parker, PCORI has already done a lot of this and so we can learn from what are some of the best practices that have already emerged that's great, but I think just let's get t-shirts made that say "Ask the patients," and I just think that's so crucial.

MR. CONWAY: Thank you.

I'll tell you what, we'll do Dr. Seelman and then we'll go to you. Go ahead.

DR. SEELMAN: The first thing I have to say is that I would've rewritten this to put the

-- eliminate the mentally and physically disabled groups, and after (b), I would've added groups with disabilities because they no longer have to be segregated. Even the National Science Foundation is collecting data in relation to increasing the numbers of stem medical math, whatever, and one of the groups that's underrepresented is people with disabilities. So I don't think we need to segregate them.

I would also say that customization is really interesting. Now with so much of our software, we can do a lot of customization. How it applies to recruiting and enrolling, I'm not sure. But, you know, people with -- although Tuskegee is an extraordinary example, people with disabilities also have a history of great distrust of the medical establishment often. In customization, if you want a deaf audience or a deaf group, you probably would want to use a video phone or something like that to communicate and we have the technology to do that. So those are the things that came to mind for me.

Thank you.

MR. CONWAY: Great.

Doc.

DR. BLACKBURNE: Rose Blackburne.

And I agree with all my colleagues' statements, and I would just sum it up maybe a little different. I think the things in parentheses apply to each of the (a), (b), (c), and (d) groups, so I think you need the flexible inclusion/exclusion in rare disease, definitely, but also in the different subgroups and disabled groups and for different age groups, and then similarly having cultural sensitivity to all these different subtypes of patients is important. Rare disease, because it's genetic, there are also ethnic populations that are affected, so you have to be sensitive to that and similarly with these different culture and teenagers and younger patients as they are with elderly.

So I think all of these things apply equally to the different groups listed. Visit burden

needs to be looked at from all of these to get patients in. So definitely for rare disease, but also to get patients in from -- all types of patients in. And that was something that we talked about all yesterday and today, how do we relieve the burden? So I don't see the separation. I think it's applicable to each group, each solution or each problem is applicable to each group.

MR. CONWAY: Great, thank you.

Cynthia and then we'll move to Deb, and then we'll have Fred speak.

MS. CHAUHAN: Cynthia Chauhan.

I am a strong believer, and the trialists are not, that the trial participants should reflect the affected population. That does not usually happen. The most recent and most obvious example of that I can think of is the cardiovascular trial world, where for a long time it was only white men and that does not translate to women or to people of other colors and races. So I really would like for us to look at that, make sure that who you're testing reflects who you want to use the device.

I wonder about reimbursement for participation, and I know that's a very hairy area, but I think it's something that it might do us well to look at if we want to engage other than well-to-do white men in our trials. The fact is trials can be a great burden on people, but if we can relieve some of that burden we'll get better participation.

Regarding flexible inclusion and exclusion criteria, I would like to add to that people with comorbidities. We are an aging population, we are a population who are becoming more and more comorbid, and we need to think about arms in trials that serve people with comorbidities because when the device or drug goes out into the world, those are the people who wind up having to use it.

Mentally challenged people, I think, is a huge issue because of our history of abusing this group of people in clinical trials, so we need to tread really carefully and really

thoughtfully there. I am not saying they should not have access to trials, but I am saying we really need to look at our history. And the same is true with the African-American population. These two populations have been abused. The Native American population has been ignored. The Native American population was at the forefront of the diabetes epidemic, but how many of them have been in trials for diabetes? So I guess I'm saying this is a hairy area that we need to really get down and dig into and look at carefully and come up with some ideas.

MR. CONWAY: Great, thank you.

MS. CORNWALL: Deborah Cornwall.

My only thing to add here is we haven't addressed rare disease populations, and I think it's probably because we don't understand enough the diversity that exists within those. And I know that there are some, particularly in the nervous system area, the neurological area, where every patient's symptoms may be different and they may differ by day and I think there is a complexity there that needs to be understood before we can offer any recommendations there. But I think it's certainly something that, given the smaller numbers but also probably the variability within their specified populations, that needs some attention and some consideration.

MR. CONWAY: Thank you.

Fred.

MR. DOWNS: Just, I think it's necessary to have data to understand how many -- how many different types of clinical trials there in different areas, and so that would develop a population that would allow you to see who's missing from it and then direct a policy or direct attention towards the areas of physicians who work with those particular disabilities or particular diseases, and so generate that interest among the physicians to provide the patient names to -- provide information to the patient and encourage them to

participate, to volunteer.

MR. CONWAY: Great. Any other comments in answer to this?

(No response.)

MR. CONWAY: I'll give my opinion, Dr. Tarver.

In looking at this quickly, my initial reaction was all of the below and all of the above, as a quick reaction. I think there are a couple of different things here that you've heard across the Panel and I'll get into that in the summary. But, in particular, taking my hat off and putting a different hat on as somebody who has worked a lot in the renal space and the cardiac space, I think one of the key things that was raised was the issue of the comorbid population and the flexible enrollment, because at least in the experiences that I've had and then some of the other larger national groups that I work with, it's an academic exercise in some ways to take a look -- and I understand the protocol issue, but to take a look at somebody with X condition and not think that they ought to have an underlying or pre-inclination into another condition or multiple things going on. And that's not just on the diagnostic or the biologic side, I think it's also on the device side, clearly, so keeping that in mind.

The other thing that I think is that you have multiple entities of the federal government that are gold mines of information and one of them that was talked about here is PCORI. So from an outside perspective, and I'll be candid, PCORI is kind of a mystifying thing to me because, essentially, the United States government created a great think tank and they've been thinking about it and writing about it for a long time. In the world that I come out of, of public policy, you can have all the great thought in the world, but if you don't operationalize it and get it out into the public sphere, what's the impact? So I come from the world of what are the metrics and what are the impacts, and if thought is being generated, then absolutely, we want to go and incorporate that and pull it in and take a

look at it, because if you go to the purpose of the PEAC, we're actually charged with taking a look at those things that are guidance, policies, registry design, so many of these different things are hardcore FDA policy issues that we're allowed to make recommendations on and I think there's a wealth of information that this Committee can pool to do that.

The other agency of the government that I think might, at a tactical level, offer some insights into this issue of recruiting and enrolling is, with no great surprise, the U.S. Department of Defense, which has been in this business for a very long time in terms of outreach, in terms of sustaining recruitment and that type of thing. And while much of that is on the financial side, there's a whole different side of that also, in terms of the populations that they reach out to and the many different organizations that they work with. And, again, I raise that from the standpoint of having background in that in DHS of how you go about actually trying to find populations. You could gather some insights from that. But I think the direct is with PCORI.

After offering those comments, I'll go ahead and say this to you, I think it's probably no surprise that there's probably definitely consensus on the Panel that (1) we would rewrite the question; (2) I'll also add the caveat that this is our initial response, Dr. Tarver, and we'll take a look at the body of everything that's come about in the past couple of days, but I think the intention of the question obviously was very positive. I think that there were many different things that were raised that we all agree on. There needs to be -- if it's true in the rest of the economy and if it's true in the rest of research that the use of targeting and outreach can be done to enhance recruitment and getting a message out and involving people, then you must also be doing that to those populations that are potentially the most impacted by disease or by injury. And I think the use of customization and all the different kinds of tactical things that we talked about are important.

But there are some overarching issues here that I think we've each touched on, some

directly; in the case of Cynthia, it is a little bit more indirectly, but that's the issue of the ethics that are involved and I don't think you can take this particular question and view it outside the construct of two things: (1) ethics, what is ethnical to do, what the patient knows, the intent for going out, what your end objective is as you're trying to recruit and retain.

And the other issue, I think, that's fundamentally important underlying this and that was raised also, is the establishment and the maintenance of and the furtherance of trust, and that's at multiple levels: (1) it's trust in government, for the FDA, and how that's sustained; (2) it's with industry, and if it's not accurate and it's not clear and it doesn't appear to be truthful, then people -- it shouldn't be a big leap for them not to believe it and I think that the onus weighs heavily, I think, on industry but also those who regulate.

I think some of the other elements of the consensus here, I think the issue that Fred raised of taking a look at data and essentially, kind of in a very basic way of where are the trials being conducted, who are we going after, how do you make that information available to them, probably would increase the likelihood of getting more people in that region or in that area to them or at least getting it better advertised. And I understand that's not completely an FDA responsibility, but I think having that in mind as we make recommendations on what's an ideal roadmap and the elements of it, it's probably quite important. If there's any dissent or anyone wants to jump in, feel free.

(No response.)

MR. CONWAY: So that's what I would propose as an initial consensus answer.

DR. TARVER: Thank you.

DR. MILLER: No. 4: What are various methods that could be used to facilitate participant retention throughout the duration of the clinical trial?

a. Would the methods be different for aforementioned groups (i.e., rare disease

population or members of different age, racial, ethnic, socioeconomic, religious, gender or sexual orientation, or disabled groups)?

MR. CONWAY: Dr. Parker.

DR. PARKER: Monica Parker.

A couple of things that stood out to me were, number one, the issue of feedback and summarization. Every time a patient comes for a visit, there needs to be some kind of exchange of information. Whether it's presaging what's going to happen during this next visit and where we are in the study, it seems that most patient participants or research volunteers want some type of summary and update with respect to their visits.

The other things that stood out to me were things that made -- were things that humanized the participants, you know, the extension of common courtesies, assistance with things like lodging, if it's going to be a prolonged study or if you were going to be in the clinic for a prolonged period of time during the day, offering them things like water and food. For pediatric patients, and I hadn't really thought about this, I thought it was neat, and said offer the young people, adolescents, some type of entertainment to keep them engaged.

And then finally, one of the things that has to do with making research participation something that's easy to do, easier, was decreasing the amount of time that had to be spent in, let's say, a research institution or a hospital versus doing some type of in-home monitoring or close-to-home kind of monitoring for blood draws or x-rays or any kind of follow-up studies. Is it necessary to travel afar to get those kinds of follow-ups? And I thought that those were basic. But I think the thing that I thought was most significant was a lot of times in research we have a tendency to forget and extend basic common courtesies to people participating.

MR. CONWAY: Great, thank you.

Cynthia.

MS. CHAUHAN: Cynthia Chauhan.

I think that, first of all, someone mentioned yesterday focusing on the patient as a human being, not just on the trial and its needs, and you touched on that, too.

I think the problem with doing some of the testing closer to home is if, for example, CT scans or x-rays are involved, those machines have to be calibrated to trial standards and the people have to be trained to trial standards, so that might be a barrier to doing that. But I think the telephone stuff, the taking an iPad home and doing QOL and PRO things, that certainly is very feasible.

I think supportive measures, and you touched on these, too. If you want to reach a broader population, we need to think about childcare, transportation, food, and possibly again bringing up the hairy thing of payment for visits. This does happen in some trials and that seems to be more at the discretion of the trial sponsors. There aren't any real ethical issues around it. So I think that makes it easier for some people to participate. Yeah, I think support and valuing of the patient as a person and if you care about people, they stay with you.

DR. PARKER: Just one thing to my comment. In terms of the feedback, listening to some of the people who testified today and some of their adverse events, if you will, the doctor in their community couldn't really help them with those sorts of things. So I think that when I talk about feedback, it's sort of like what kinds of complications should I be looking for and who can address those things. So it would be helpful in those instances if I'm getting a procedure in an academic center, that whoever my primary care doctor is, she'd be made aware of what the likely complications are and how to help this patient follow up with whatever it is he or she is seeing. And I thought that was horrible to have something happen -- well, I've experienced it in my clinical practice, people come and they

have a complication and it's sort of like, well, I don't really understand what to do with this, particularly when people have gone, for example, to a foreign country to have a surgical procedure and it's like you're not aware of it, but you're the first person that they see.

So I think that if people are involved in clinical research studies, whoever their primary doctor is or their gynecologist or their cardiologist is, their treating cardiologist needs to be aware of what study you are participating in and how best to monitor for adverse events. And that, again, brings the issue of bringing the treating physicians, making them partners in this whole enterprise.

MS. CHAUHAN: Cynthia.

I agree with you. And the trialists -- the trials I've been in, my trialists always tell me to be sure to take -- they give me a card about the study, to take that to my primary physician and share that with them. So I think an emphasis on that sharing would be very supportive of patients and might help avoid some of the terrible things that we heard about.

MR. CONWAY: Go ahead, Doc.

DR. BLACKBURNE: Rose Blackburne.

And I, again, agree with what Dr. Parker and Cynthia said so far. I would add that what we've learned over the past day and a half is that the patients will tell you what will retain them. And I say this as a follow-on of the first three questions. What got them in will likely keep them in if we got their true input from the beginning and meaningful input about what will keep them, what's convenient, what makes sense, what's doable, how do we decrease the burden. So all the things that we covered specifically in Question 3, but in the other questions, as well, I think apply to what will retain them for the duration of the study and keep them engaged.

MR. CONWAY: Okay, thank you. We'll go to Fred and then Dr. Seelman.

Just as a reminder to the Committee, we have one more question to answer and to wrap, and then we'll move to conclude the meeting.

Go ahead, Fred.

MR. DOWNS: Fred Downs.

My blood sugar is low, but I've got a few things here.

(Laughter.)

MR. DOWNS: It's in support entirely of what's been said before except I just want to say humanize the feedback. Make sure the family is involved in that feedback because -- and then how is that going to be provided to them, in a big stack of papers? Is it a summary sheet? Whatever. So just keep it simple for the patient and make sure the patient's family is involved in each stage of that process so they know what's going on, too.

MR. CONWAY: Great, thank you.

Go ahead, Doctor.

DR. SEELMAN: I think that this concept of customization is very applicable here, and I could even see a charter of some kind where some of these groups clearly need things that some of the other groups don't. For example, a Muslim woman might prefer a female physician. A deaf person would need X, Y, and Z. So in any case, I think that you might even be able to flush something like that out, which would be interesting and maybe it's too controversial. I don't know.

Anyway, my second one is that we're in a great moment of information flow. Too much of a moment of information flow. But nonetheless, okay, so let's say we're doing a clinical trial of electric wheelchairs to find out whether or not -- how we can improve our recommendations for regulations and standards for side bars. So we're actually getting data from these guys in real time and that's really great. At the same time, it's a potential for adverse effects right there and maybe would change or further enhance your concept of

how you collect that kind of data, especially from consumers or patients. So I think the information flow thing is really very interesting. I mean, it's something we didn't have before and we have it, for better or for worse, any time day or night.

Thank you.

MR. CONWAY: Great.

And the last comment, Amye.

MS. LEONG: Amye Leong.

Let me just play off of what Kate has previously said and take that a little bit, another step further. If we are ideally, and I know this is real-world stuff, but ideally having a patient advocate on a steering committee from the ideation phase going forward, in some scenarios I have seen and actually have been a person that almost acted like a triage for participant patients, so that participant patients -- and I'll just use a real-world case -- were not sure that they should mention this to the doctor, were not sure that it warranted any kind of concern, but when they knew that they could talk to someone like them, meaning another patient or a patient advocate, someone on the design team, if you will, there was a more readily, almost like a support group environment. I think I'll ask and see if this warranted to move it forward, to move an adverse event or a side -- who knows what the name of it is, "it" forward because I don't know what to call it, I don't even know if it's related to the disease or to the XYZ medical device that I'm participating in, in a clinical trial.

But once that person had a conversation, albeit very brief, with a member of the patient engagement responsible person on the design team, it was immediately triaged to the doctor. In one case it was not, but in most cases it was and that person felt much more confident, the participant felt much more confident to bring it forward, to then actually get into the depths of describing it, the timing of it, what their -- you know, what their lifestyle was like before it, after it, those kinds of things.

So I raise the concept of utilizing that patient engagement expert, that faith-based, community based patient advocate leader as a part of the design team, as someone at times that might be available. Of course, this is -- that has to be all worked out -- that could be available to study participants to help them better categorize what their next action would be, therefore helping in some sort of retention or action as a part of the trial.

MR. CONWAY: Okay, thank you.

I'm not going to add any comments to this question. I think the folks on the Committee have reflected everything that I was thinking about and much better than I was.

But, in summary, I'd say that the top-line answer to this question is treat people as you would want to be treated in the simple basics, the human decencies of interpersonal interaction and respect for another human being and another individual, and maybe even a little bit more, understand that that person's going through something as a patient.

And I think the issue of support, a lot of these disparate issues were raised, but transport for the childcare, lodging issues, and I think all of those things remove barriers and make it easier.

In terms of one of the issues that stood out, and I think it was a great point that Dr. Parker brought out, is what do you do in an emergency situation and is that clearly explained for people, because I think you're doing a favor for the patient, but not only that, you're doing a favor for the emergency room, where they may end up crashing into their regular medical team.

A couple of things going back to this issue of what's decent for the person: listening to them, considering how you communicate with family members and making certain that it's really clear, because oftentimes the patient may be willing, but their support unit may not understand and may not be that enthusiastic about it.

Dr. Seelman brought up a really good recurring issue, which I think should populate

all of these discussions, and that's the use of real-time data and whether or not you can actually incorporate that data and change the trajectory of where you're going at certain points based on what you're learning in real time. And I know the FDA has done work on that, but I think that's something that this Committee will be taking a look at moving forward.

And a last point that Amye made, I think, is kind of a commonsense type of thing that industry ought to take a hard look at and that we will, I have a feeling, probably recommend it at some point, but that is when you're designing something, make certain there's somebody there that can speak to you that's of a similar situation or at least know what it's like to be in your shoes, and whether you call them an advocate or an ambassador, make certain they are part of the process and the patient can actually go to them.

So if we could go to the next question, and I know that we're coming up on the schedule. If you folks could take a look at this because there is time here to make some initial recommendations on topics and I want to make certain that each person has the opportunity to talk about topics for future meetings. But in regard to this particular question here, any quick thoughts going around the table?

Suzie.

MS. SCHRANDT: Yeah, I'll just recycle -- Suz Schrandt, sorry.

I'll just recycle two of my answers from before, because I think they're really applicable here and that's really thinking upstream, meaning the time to plan for dissemination is not the end of the trial, it's the beginning of the trial, and ask your patients, do this in concert with the patients.

A quick story from a PCORI-funded study that was well publicized at the very front end, but there was a whole steering committee, I think, of patients that were helping design the trial. One of the outcomes they selected -- this was a stroke study. One of the

outcomes the patients selected was days spent at home, so outside of the hospital or outside of an institution. The outcome that the clinicians and researchers had selected was recurrence of stroke. And so those are not quite the same, you know, outcomes. The idea is having patients involved at the front end paves the way for your dissemination because, though it's time to share results, you have already made results that actually speak to patients. So when they started getting results and then they could say, you know, this particular drug used in this context increased days spent at home, that actually meant something to patients, it was contextualized. So just again, upstream, and it's got to be in concert with your patients.

MR. CONWAY: Okay. Great, Suzie.

Cynthia.

MS. CHAUHAN: Cynthia Chauhan.

My inner troglodyte comes out. I think that the methods, social media, email blasts, text and brochures, not so much brochures, but the others are fraught with danger. They are usually brief and open to multiple interpretations. I agree strongly with what Suz said, don't think about this at the end, think about this from the beginning and engage patients in talking about it. Newsletters during and throughout the trial are a good idea. I'm engaged in the PCORI -- count trial and we send out newsletters regularly to the patients who are in the trial. So I think that can be very helpful and that goes to valuing the patient also.

I own that I have issues around participant involvement in communicating results to others. I think there are real issues here around patient confidentiality and patient privacy and sometimes people are very willing to do something without thinking about the long-term consequences for themselves and I believe that the trialists have a fiduciary relationship to the patients to think about long-term consequences and to make sure

patients are aware of that. So I think that's a really tricky area.

Timing: I think final results to patients are extremely important. They should be personalized, a patient should get a personal letter telling them the results, what it means to them, and I like a copy of the published data to be a part of that, wherever the article went, to *JAMA* or to *ASCO*, wherever.

So putting together newsletters about things as things are going along and then final results to the patients and again, to the participants and again, hopefully you will have instructed them from the very beginning that length of trial is different from length of participation, so they know this may come farther down the line.

MR. CONWAY: Any other brief comments on this?

Okay, Bennet.

MR. DUNLAP: Very briefly. I think it was interesting today that we had a presentation that said well, nobody thinks about including communications design at the outset because it's expensive and yet, at the same time, people said well, it's expensive to recruit people and retain people. Well, maybe designing your communications up front, as our friend Suz suggested, is a really good idea.

MR. CONWAY: Great.

Amye.

MS. LEONG: Having come off of the NIH -- I'm really tired, sorry -- advisory panel, one of the things prior to Dr. Francis Collins coming on to NIH, the advisory group came up with -- tried to include a better way to share information coming out of NIH to the general public with almost zero budget. And so given that there are 17 institutes that comprise the National Institute of Health, we all devised a concept called the NIH moment, 60 seconds, and I mean 60 seconds over the radio, of very plain language information, very top line, but then that would take you to the NIH website, which on the landing page would have the NIH

moment not only in the short sentences that comprised that radio 1-minute PSA, public service announcement, but then drill down to the actual studies, themselves.

And so I was actually caught off guard by driving down the highway one day in California and had to pull over off the road because I was so excited to hear about NIH on the radio and found out that other people were hearing that and were thinking wow, my tax dollars at work. It caught people's attention.

So this is not a standalone item, but this is something that's in a communication strategy, and I'm really talking about a total communication strategy, has to be looked at, at a systems level but then has to have a complement to it that is a requirement or recommended way within each of the clinical trials programs.

MR. CONWAY: Great, thank you.

And, Dr. Parker, the last comment.

DR. PARKER: The last comment. I just wanted to stress the amount of the same things that people have said with respect to literacy and different methods if you do have to, again, meet people where they want to be met. And because I deal mostly with older Americans, all older Americans aren't on a computer, so we have to use -- what did you say? Troglodyte. We have to use older methods of communication to different people.

But the other thing that I wanted to say with respect in communicating clinical trial results, somehow or other we've been talking about doctors and patients but we haven't really been talking about investigators, and it should be incumbent upon the investigator to create his or her method or way of doing that and that shouldn't be left for us to come up with. Whoever the investigator is should have that as part of what he or she does. I mean, we haven't talked about the investigators or the industry or whoever the funder is. They bear some responsibility for getting this communication to the general public out.

MR. CONWAY: Great. I'll just say one thing and it's already been said by everybody.

There's an old law in messaging and in communications, and I agree with the strategic standpoint. It's message times frequency times platform times repetition equals result, take result and then drive it back out across all platforms again. And industry uses it, commercial sector uses it. I think it's a similar type of thing here.

In terms of some quick points on these issues, I think many of the answers to Question 5, in summary and responding to you, Dr. Tarver, in terms of the answer, many of the answers for Question 5 have been answered in some of the other questions that have been posed but I think, again, making certain that message can go out, that it's clear, that it's reaching multiple audiences, that it's done within a strategy. I think all of those things are very important. And I think Fred's point of it's the law of K-I-S, keep it simple, and then making certain that the feedback is there and clear. I think those are all important elements of this, but I think this particular question actually is one of the things that, again, when we take a look at the base of the information coming off the round tables, we'll have some reflections on that. If I could, I would submit that as my summary to Question 5.

DR. TARVER: Thank you.

MR. CONWAY: I'd like to pose a question to you. In terms of process, the next thing on the agenda, and I think it's an important one and we can do it fairly quickly, committee members will make some recommendations on future topics. Absent of being in the room and recommending those, what's the process going forward for getting those to FDA by the Committee? So if we wanted to suggest future topics, we can go ahead and do that now and then on an ongoing basis, who would we suggest those to?

DR. TARVER: So we'll welcome any comments that you have right now, if you'd like to discuss them in the time that remains. And then in the future, if you would like to send them in, you're free to communicate with Letise Williams, who is the DFO, and we can collect that information.

MR. CONWAY: Okay, thank you.

So initially here, before we go ahead and wrap up, any thoughts over the past 2 days about future topics? And these can be one-word, two-word, or concept, but I think going ahead and throwing them out there if you have any that you're thinking about.

Fred.

MR. DOWNS: I think the two patients today, or three people who spoke about the lack of trust or communication to the FDA, I'd be interested in knowing what the process is, what kind of mechanism is set up so they can communicate back with those patients, and are these real problems or not. And so who does a patient go to if there are problems with FDA and what kind of response is there and do they keep data on that kind of issue or problem from across the nation? I would like to know more about that.

MR. CONWAY: Okay, thank you.

Okay, Deborah.

MS. CORNWALL: I have only five. One of them is the process for adverse events, I think, needs further exploration and refinement.

I think, secondly, we should spend some time talking about the whole culture change, congruence of values, and broader stakeholder education challenge because I think there are areas where we should be offering some, at least, framework guidance perspective on that and exploring how that can be done better.

Third, I think there's an issue around data privacy. There were some concerns expressed in terms of personal data. I think there are also some issues around the hack-ability, if you will, of equipment that people -- devices that people are wearing or are implanted that are giving out, you know, information about their personal health status and ensuring that there is some protection built in, in terms of the privacy of that data.

There was certainly a comment -- fourth -- that was mentioned yesterday in terms of

a clinical trials playbook. There may be some guidance that we can offer in terms of how -- the key variables that ought to be addressed, for instance, by the individual investigators and so on.

And then finally, I think the issue of how we engage the PCP and the medical community more in the clinical trial process so that it's not just the investigators and just the people who are directly associated with the trial needs to get some attention.

MR. CONWAY: Okay, thank you.

Any other suggestions? We have vehicles for making that.

Sorry, Doctor. Go ahead.

DR. BLACKBURNE: Rose Blackburne.

I'm reiterating and agreeing with what my colleagues have said. I would like to see a more expanded discussion around how can we better educate all clinical trial stakeholders about clinical trials, so how can we drill down on each component of the trial and educate people better so they understand what they're getting into, and I think that would drive recruitment and retention and data dissemination.

And then I'd like to see us drill down more on how we can reduce the patient and the family burden of visit burden, so maybe discussing more about telemedicine or technology, home visits, all the things that can reduce visit burden. And then also I'd like to see how we can talk more about safety concerns.

MR. CONWAY: Great, thank you.

Amye.

MS. LEONG: I believe this was mentioned yesterday. The days are getting confusing to me. It was specifically about the engagement of patients in the development and standardization of measurement, of measurement tools, and I'm talking about core outcome sets, PROs, just that whole arena for which clinical trials, quite frankly, are basing

a framework upon. And drilling down into how this becomes meaningful for patients, if we don't have measurement sets that, for which patients or patient reps have not been involved in, how reliable is that, how realistic is that, and then all the data that comes from that, how convoluted we get with respect to that.

So I know we're talking about a very complicated area, but I think it's important that we, as a PEAC, come forward with recommendations in regard to that, because there are agencies and bodies whose sole purpose is to do that, but do they engage patients? And certainly, comments and recommendations from this body would be very helpful.

MR. CONWAY: Okay, thank you.

Dr. Tarver, would you like to make any concluding comments?

DR. TARVER: I just want to thank everyone for their thoughtful insights and the participation of the audience in this meeting.

MR. CONWAY: Thank you.

MR. DUNLAP: Paul, I had one last comment.

MR. CONWAY: My apologies, Bennet.

DR. SEELMAN: I did too, after he goes.

MR. CONWAY: Okay, great. Rapid fire.

MR. DUNLAP: Sorry to make everybody wait and I'll try to be quick. We saw the total product life cycle chart from FDA, from CTTI, and it ends with postmarket, and I think there needs to be another block on that; that is enforcement. We're in an environment where a device -- devices are evolving rapidly and guidance is advancing as technology advances, and if we have products that are still on the market that were approved to old standards, they shouldn't still be on the market. It's like saying hey, you know what, we're going to let the Chevy Corvair be produced even while we have, you know, the guidelines now for, you know, cars with good airbags and they're safer cars and I'm trying to make an

analogy that is not in the medical space, but we need to get older products, that they're life cycle is over, respectfully off of the market.

MR. CONWAY: Okay.

Dr. Seelman.

DR. SEELMAN: This is kind of a repetition of some of the things I've already said, the value added of patients and consumers. The unique issues that occur because we're dealing with devices, not drugs, and the integration related to that and to the consumer, patient, the integration, how do we integrate these issues related to quality of life, ADLs, usability in particular, since it is unique to the integration of people with disabilities in clinical trials?

And this mobile technology usage and impact certainly does seem, to me, impact almost at every stage of clinical trials, or could.

And, finally, this problem that was brought to us constantly today from people, adverse event reportage, I mean, and the pathways that the FDA could have or does have to hear people who may not be immersed in science, but certainly have had a lot of experiential experience with these problems of adverse effects.

MR. CONWAY: Thank you.

At this point, I would like to thank all those who joined us over the past 2 days at the inaugural meeting of the -- oh, my apologies. No, go right ahead.

MS. CHAUHAN: Just one quick thing. There's an underlying thought in many cases that trials in devices are not as rigorous as drug trials and I would like, at some point, for us to have some feedback from the FDA on whether that is true or it's just a rumor that got started that goes on, because if it is true, then that's an area that we can certainly have an impact in. Sorry.

MR. CONWAY: Oh, no. No, no. That's never a problem, Cynthia.

But again, I'd like to thank everybody over the 2 days who's been with us. This is the inaugural meeting of the PEAC. And I'd especially like to say thank you, in that we understand the efforts that the FDA's Center for Devices and Radiological Health went through to bring today together and to make this possible and for our journey going forward.

The participation by those on the Committee today, and those in the audience and those who have joined us online, is an initial step in the continuing effort to develop patient-friendly clinical trials to help assure the needs and experiences of patients are included as a part of the FDA's regulation of medical devices and their use by patients. We ask that you consider completing the survey shown at the link on the slide, so that we can get your feedback on this meeting and inform how we conduct future meetings.

This meeting of the Patient Engagement Advisory Committee is now adjourned with one caveat. I'd like to thank the hotel staff and the restaurant staff for making themselves available to us; the tech team throughout the past 2 days; the transcriptionist for keeping up with us and all the things that I jumped over; and Letise Williams, who has been a pinch hitter and great support to me as the Chair of this; and, of course, to the FDA: to Katie O'Callaghan, to Dr. Shuren, and to the Commissioner. I think your efforts are sincere and we're happy to be a part of it, and sometimes we might go off the rails a little bit, but it will be out of sincerity and interest in patient safety and helping you fulfill your mission. So thank you very much.

The meeting is now concluded.

(Whereupon, at 5:00 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

PATIENT ENGAGEMENT ADVISORY COMMITTEE

October 12, 2017

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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Official Reporter